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REVIEW

Application of the cortical bone trajectory technique in posterior lumbar fixation

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Abstract

The cortical bone trajectory (CBT) is a novel technique in lumbar fixation and fusion. The unique caudocephalad and medial-lateral screw trajectories endow it with excellent screw purchase for vertebral fixation *via* a minimally invasive method. The combined use of CBT screws with transforaminal or posterior lumbar interbody fusion can treat a variety of lumbar diseases, including spondylolisthesis or stenosis, and can also be used as a remedy for revision surgery when the pedicle screw fails. CBT has obvious advantages in terms of surgical trauma, postoperative recovery, prevention and treatment of adjacent vertebral disease, and the surgical treatment of obese and osteoporosis patients. However, the concept of CBT internal fixation technology appeared relatively recently; consequently, there are few relevant clinical studies, and the long-term clinical efficacy and related complications have not been reported. Therefore, large sample and prospective studies are needed to further reveal the long-term complications and fusion rate. As a supplement to the traditional pedicle trajectory fixation technique, the CBT technique is a good choice for the treatment of lumbar diseases with accurate screw placement and strict indications and is thus deserving of clinical recommendation.

Key Words: Cortical bone trajectory; Management of midle line fusion; Lumbar interbody fusion; Lumbar surgery; Review

Core Tip: The cortical bone trajectory (CBT) has obvious advantages in terms of surgical trauma, postoperative recovery, prevention and treatment of adjacent vertebral disease, and the surgical treatment of obese and osteoporosis patients. This review presents the biomechanical characteristics, the perioperative osteoporosis management of midle line fusion (MIDLF) surgery, the clinical effect of MIDLF when comparing to other lumbar fusion surgery, the clinical effect of MIDLF for the treatment of lumbar spondylolisthesis, the advantages about MIDLF for spinal revision surgery, and the computer navigation-assisted CBT technique.

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INTRODUCTION

Since its first use for stabilizing the spine segment six decades ago[1], pedicle screw (PS) fixation has been widely applied and popularized due to its desirable biomechanical properties and high fusion success rate. It is considered to be the main surgical method for spinal fusion and fixation[2-4]. The traditional trajectory for PS insertion is from lateral to medial, which corresponds to the anatomical axis of the pedicle and is parallel to the endplate in the vertebral body. However, to longitudinally arrange the screws on the left and right sides with a focus on convergence, the muscles and soft tissues must be widely retracted, which will increase muscle injury and prolong the recovery time. Especially in patients with osteoporosis, maintaining the stability of internal fixation is a major challenge. When PSs are embedded in cancellous bone with low pedicle density, they can be easily loosened, removed or broken, resulting in poor surgical effects and even complications. The fixation strategies for low bone mass are mainly divided into: (1) Modifying the implant design, such as changing the length, pitch, and thread depth or expanding the diameter of the screw; and (2) Strengthening the vertebral body with reinforcing materials, such as assisted fixation with bone cement, to improve the structural strength of the osteoporotic bone. However, the use of screws with larger diameters and lengths will lead to a doubling of the risk of injury to nerves and vessels, and the use of bone cement is associated with risks of bone cement leakage and spinal canal nerve compression, leading to more disastrous consequences. A computed tomography (CT) study of pedicle bone density conducted by Hirano *et al*[5] revealed that the pyramidal cortex of osteoporotic bone is thinner than the normal cortex, and the bone mineral density of subcortical bone is low. Increasing the screw diameter does not improve the stability of the screw and may even lead to extraneous fracture of the thinned pedicle cortex. Therefore, a new internal fixation system is urgently needed to solve this problem.

To solve the major problem of effectively fixing vertebrae with low bone mass, based on the idea proposed by Buck and attempted by a group of surgeons[6-8], an alternative screw trajectory was reported by Santoni *et al*[9] and gained increasing attention in 2009. This novel trajectory has a caudocephalad direction in the sagittal plane and a medial-lateral path in the transverse plane (Figure 1). With this new trajectory, the mechanical stability and pullout strength of the screws were significantly improved by including 4 Layers of cortical bone, including the starting point, the inner wall of the pedicle, the upper wall of the pedicle and the outer-upper wall of the vertebral body; hence, the trajectory was called the "cortical bone trajectory (CBT)". The screw designed by Santoni *et al*[9] is shorter and has a lower diameter and a tighter thread than the traditional PS, all of which aim to maximize the thread contact with this higher density bone surface to increase vital biomechanical parameters.

Based on the application of CBT screw fixation, Mizuno *et al*[10] first proposed the concept of midline lumbar fusion (MIDLF) in 2014. In this original procedure, single segment spinal canal decompression, discectomy, interbody fusion and cortical screw fixation are all completed through a small midline incision, minimizing the injury related to the approach and providing another choice of fusion internal fixation for the clinical treatment of lumbar diseases. Over time, surgeons have applied CBT screws through a middle incision to fix two or more levels, which, combined with transforaminal lumbar interbody fusion (TLIF) or posterior lumbar interbody fusion (PLIF), has also been defined as MIDLIF [11-13]. Although many researchers have described techniques with names such as CBT-PLIF or CBT-TLIF, they were in fact instances of MIDLIF[14-18].

Although MIDLF also involves separation of the paravertebral muscles along both sides of the spinous process, unlike in traditional TLIF or PLIF, only exposure of the inner edge of the articular process and the vertebral lamina is required, and the relatively large distance between the screw entry point and the articular process helps to protect the articular process joints.

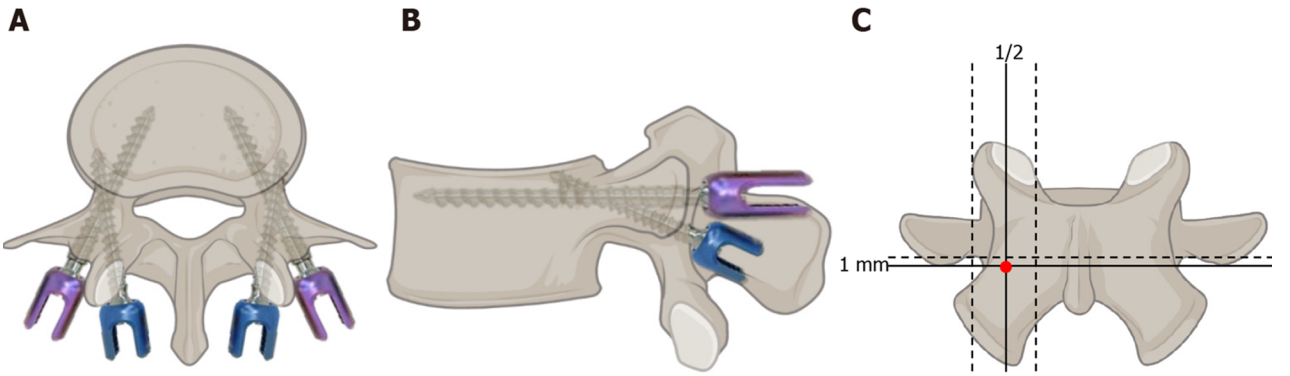

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Figure 1 Schematic demonstrating cortical bone trajectory screws (purple) and pedicle screws (blue). A: Axial view; B: Lateral view; C: The ideal insertion points of a cortical bone trajectory screw (red dot).

BIOMECHANICAL CHARACTERISTICS AND IMAGING STUDY OF THE CBT TECHNIQUE

In 1986, Steffee *et al*[19] proposed the term "force nucleus", which refers to the focus point of the pedicle, lateral pars, lamina, transverse process and superior articular process. This area has a high concentration of cortical bone, so it can provide a strong screw holding force. In 2004, Li *et al*[20] found that the medial and superior pedicle isthmus cortex (more than 2 mm) was thicker than the lateral and inferior pedicle isthmus cortex (less than 2 mm), providing a stronger holding force for the screw than the lower and outer walls of the pedicle. In 2009, Santoni *et al*[9] proposed the CBT fixation technique and first analyzed its biomechanical properties. The results showed that CBT screws provide a 30% increase in uniaxial yield pullout load over traditional PSs and have similar flexion and extension resistance to PSs. Another notable result was that the type of CBT screw required did not depend on bone quality, which means it was suitable for osteoporosis patients, similar to the findings of other studies[21-25]. In 2014, Matsukawa *et al*[26] first reported that the insertional torque of CBT screws is approximately 1.71 times higher than that of traditional PSs.

Ueno *et al*[27] found that the maximum pullout strength of CBT screws in pig lumbar vertebrae was significantly higher than that of traditional pedicle cancellous screws. Oshino *et al*[28] concluded that the intervertebral stability after CBT fixation was similar to that after PS fixation. Delgado-Fernandez *et al*[29] found that CBT screws exhibit greater stiffness in cephalocaudal and medio-lateral loading, better flexion and extension resistance and better screw-holding stability in the pullout strength than traditional PSs; however, CBT screws were inferior in terms of lateral bending and axial rotation; these findings were confirmed in recent studies[24,30-34].

Mai *et al*[24] found a higher bone mineral density (BMD) for the CBT path than for the traditional pedicle trajectory path through CT examination of the lumbar vertebrae of 180 patients. Therefore, CBT screw purchase may be sufficient to stabilize the spine in osteoporotic patients. Another radiological evaluation performed by Kojima arrived at a similar conclusion[35]. The mean CT number [Hounsfield Unit (HU)] for CBT was more than four times that of the traditional pedicle trajectory. This is in keeping with previous hypotheses that the new trajectory offers. A previous study found that among 470 adult lumbar vertebral specimens, the CBT screw bone channels showed no significant differences in the diameter, length, or angle with the sagittal and transverse positions of the vertebral body; thus, the researchers concluded that the lumbar CBT screw bone cortex channel has a stable anatomical structure and small dissection variation[36]. Perez *et al*[37] found that the strength of CBT screws in lateral bending was significantly lower than that of PSs. Ninomiya *et al*[38] showed that the average insertion torque of the vertebral bodies of patients with spondylolysis was significantly lower than that of the vertebral bodies of patients without spondylolysis. In addition, the authors found that the average insertion torque of CBT screws in women over 75 years old was low and that CBT internal fixation was not suitable for 75-year-old women with spondylolysis. Matsukawa *et al*[36] performed a biomechanical study and showed that CBT is not suitable for patients with lumbar spondylolysis, mainly due to anti-flexion stretching and poor rotation compared with traditional PS fixation[39].

Given that CBT screws demonstrate lower lateral bending and axial rotation than traditional PSs, new attempts at developing combination strategies have been reported. Cornaz *et al*[40] suggested that a cross-connector could be beneficial for increasing the anti-lateral bending or axial rotation properties of CBT screws; however, there is no increased necessity to use a cross-connector in a CBT construct. Matsukawa *et al*[41] found that the combined use of traditional trajectory and CBT screws offered superior fixation strength over the traditional trajectory and CBT techniques in each plane of motion. Kahaer *et al*[42] and Mullin *et al*[43] also found that using a combined CBT and traditional pedicle trajectory offered superior fixation strength over that of the individual trajectories alone. This may be

because the shorter length of the original CBT screw designed by Santoni *et al*[9] cannot provide sufficient fixation strength for the vertebral body, whereas the intervertebral space is the main structure for bending or rotation. Therefore, the original CBT screws not only provides less strength for anti-lateral bending or axial rotation but also may decrease the fusion rate for the interverbal body. This was demonstrated by Matsukawa *et al*[44] in 2 studies. In the first study conducted in 2016, they found that the screw length within the vertebral body (% length) was more important than the total screw length and that the screw should be placed sufficiently deep into the vertebral body. Then, in a study conducted in 2021, they identified that %depth > 39.2% was a predictor of bone fusion (sensitivity 90.9%, specificity 75.0%), that is, that the depth of the screw in the vertebral body should be at least 39.2% to achieve a stable fusion rate[45].

CBT SCREW PLACEMENT METHOD

The CBT screw placement method differs from the traditional trajectory screw internal fixation method in a number of ways. The first difference is the screw entry point, which in the CBT is located much more medially than in the traditional trajectory. Mobbs's study first described the nail placement path in the CBT[46]: After the nail insertion point is selected inside the isthmus, holes are drilled with a 2 mm grinding drill to establish the nail insertion channel, and the screws are inserted to point from the tail side to the head side and finally end at the rear 1/3 of the upper endplate to minimize the risk of isthmus fracture. However, this study did not indicate the standard trajectory for CBT screw implantation. Matsukawa *et al*[47,48] showed that the ideal insertion point of a CBT screw is the intersection of the vertical line passing through the center of the superior articular process and the horizontal line 1 mm below the lower edge of the transverse process. They found no significant difference in the angle of insertion from Lumbar 1 (L1) to L5; the head angle was 8° to 9°, and the abduction angle was 25° to 26°. The diameter of the screw varies according to the width and shape of the L1 to L5 pedicle and is generally smaller than that of the traditional PS. The diameter of the screw channel is 6.2 to 8.4 mm, and the depth of the screw is 36.8 to 38.3 mm.

In conclusion, most researchers believe that the ideal starting point is at the junction of the 1 mm horizontal line at the lower edge of the transverse process and the vertical line in the middle of the superior articular process. The point was specifically located projecting in the 5-o'clock orientation in the left pedicle and the 7-o'clock orientation in the right pedicle under fluoroscopic imaging[26,36]. Another difference is the trajectory path. Most researchers have concluded that the ideal screw path is at a 25° to 30° inclination from caudal to cephalad and at an 8° to 20° inclination from medial to lateral[9,10,49,50]. Additionally, the length of the CBT screw is 25 to 40 mm, and the diameter is 4.0 to 7.8 mm[44,51-54]. The angle and path vary greatly, possibly because of variations in the lumbar vertebrae from person to person due to, for example, ethnicity and the degree of lumbar degeneration, which make it difficult to develop an ideal, standardized trajectory.

PERIOPERATIVE OSTEOPOROSIS MANAGEMENT OF MIDLF SURGERY

To date, few articles have discussed the perioperative osteoporosis management of MIDLF surgery; therefore, we will describe existing management methods combined with our experience. For osteoporosis patients who undergo MIDLF surgery, it is very important to avoid excessive lying-in bed, as it will result in accelerated bone loss. Based on the excellent purchase of CBT screws and the reduced tissue damage, patients are advised to perform out-of-bed activities 48 h postoperatively and avoid standing or sitting for long periods of time during the first month[55]. The thoracolumbosacral orthosis should be worn for 6 mo postoperatively[56], and the patients will be able to resume normal activities 3 mo postoperatively. Postoperative intravenous analgesia is typically unnecessary due to the low amount of intraoperative trauma; for those patients who do experience postoperative pain, celecoxib is sufficient. However, when considering the poor anti-lateral bending and axial rotation properties of CBT screw fixation, patients should avoid lumbar lateral bending and rotation, especially when getting up from a seated or supine position. Patients are advised to wear the thoracolumbar orthosis when lying in bed and then get up from bed. Other common management strategies are similar to traditional lumbar fusion surgery, such as standard anti-osteoporosis treatment, prevention of deep venous thrombosis, straight leg lifting exercises to avoid adhesion of the nerve root in the spinal canal, incision care and postoperative radiographic imaging examinations.

MIDLF FOR LUMBAR SPONDYLOLISTHESIS AND COMPARATIVE STUDIES ON TRADITIONAL LUMBAR FUSION

Although MIDLF has been widely used in recent years and has achieved good clinical efficacy in lumbar spondylolisthesis, it was initially controversial. From 2014-2016, some of the first articles highlighted good results from this procedure, including better safety and effectiveness[57,58], less multifidus muscle damage and blood loss[59], shorter operative duration and hospital stays and less postoperative pain than traditional pedicle trajectory surgeries[61,62]. Conversely, others have focused on postoperative complications, including pseudarthrosis caudal adjacent segment failure, screw loosening[63], intraoperative pars fracture[64], and pedicle fracture[65]. The contrasting results may be related not only to the small size of the studies, the necessary learning curve and the experience of the surgeon but also to the patient's individual factors, such as nerve and surrounding tissue adhesion and local anatomical structure variation. Therefore, it is urgent to perform a randomized comparative study to identify the effectiveness of MIDLIF.

The first prospective, randomized, noninferiority, comparative study between MIDLIF and traditional lumbar fusion was published by Lee *et al*[66] in 2015. A total of 79 patients were enrolled and randomly assigned to the PS group or CBT group. Similar fusion rates were observed in both groups at the 6- and 12-mo follow-ups. According to the clinical outcomes, CBT provided similar improvements in pain amelioration and functional status over traditional PSs. Additionally, CBT was superior to PS in terms of blood loss, operative duration and incision length. The same authors then published a consecutive study on the same group of patients at the 2-year follow-up in 2018. The results demonstrated that there was no statistically significant difference between the groups in terms of clinical outcomes, radiologic outcomes and related complications[67].

Over time, some large series on MIDLIF have been published, mostly regarding lumbar spondylolisthesis. The main purposes of these articles were to compare the fusion rate, recovery scores such as the Japanese Orthopedic Association (JOA) score, the visual analog scale score and the Oswestry Disability Index (ODI) and the incidence of adjacent segment disease (ASDs) and complications. Sakaura *et al*[68] compared 95 patients who underwent MIDLIF to 82 patients who underwent traditional PLIF. Although there were no significant differences in the fusion rate between them, the JOA score and incidence of symptomatic ASDs in the MIDLIF group were significantly more favorable than those in the traditional PLIF group. Mori *et al*[69] also found that MIDLIF exhibited a significantly lower ASD incidence than traditional PLIF in a comparative study that enrolled 52 consecutive patients with single-level lumbar spondylolisthesis. Other studies on MIDLIF for lumbar spondylolisthesis also showed better results than traditional PLIF, including a shorter operative time, lower blood loss and shorter length of stay, while the fusion rate showed no significant difference[15,70].

Most of the literature on MIDLF for lumbar spondylolisthesis aimed to analyze grade I to II spondylolisthesis, and there have been few publications about high-grade spondylolisthesis. Although low-grade spondylolisthesis seems more common than high-grade spondylolisthesis, this may be due to a lack of suitable instruments for reducing severe spondylolisthesis.

Takenaka *et al*[71] studied 119 consecutive patients with a minimum 1-year follow-up. There were no significant differences in operative duration or fusion rates, whereas the MIDLIF group experienced significantly less blood loss and lower postoperative creatine kinase levels than the PLIF group. Matsukawa *et al*[72] performed a retrospective cohort study aiming to find a predictor of screw loosening. He found that the regional HU values of the screw trajectory were more strongly correlated with the insertional torque than the femoral BMD and lumbar BMD, and the incidence of screw loosening was 4.6%. Multivariate logistic regression analysis revealed that the regional HU value was an independent risk factor that significantly affected screw loosening. Lee *et al*[73] compared the CBT and conventional pedicle trajectory techniques in terms of proximal adjacent segment pathology after lumbar fusion. Among 53 patients enrolled in this study, the postoperative fusion rate was not significantly different at the 1-year follow-up, while CBT exhibited superior satisfaction at 1 mo and lower pain intensity within 1 mo, blood loss, operative time, hospital stay and incision length. This study suggests that CBT can be a viable alternative to conventional PS surgery.

Other comparative studies have aimed to investigate the results between MIDLIF and other traditional minimally invasive surgeries, such as percutaneous PS placement[74-76], microendoscopic laminotomy[77] and minimally invasive (MIS)-PLIF or MIS-TLIF[78].

Bonis *et al*[74] reviewed 72 consecutive patients treated with percutaneous PSs (PPSs) and CBT screws and showed that pain significantly improved in both groups. The Charlson Comorbidity Index was the only variable associated with an increased risk of complications. Patients with a body mass index (BMI) ≥ (median value) and patients with percutaneous screws had an increased risk of a worse Smiley-Webster Score. Patients with a BMI ≥ 27.4, patients with percutaneous screws and patients with more comorbidities showed a higher risk of presenting with a severe/crippling ODI. Maruo *et al*[75] compared the clinical outcomes after TLIF using CBT or PPSs in 77 patients and found that the CBT group showed significantly lower serum creatine kinase (CK) levels and numeric rating scale scores on postoperative days 1 and 3 than the PPS group. There were no significant differences in cage subsidence, screw loosening, or fusion rates between the groups at the 1-year follow-up. Another study

performed by Inoue *et al*[76] compared traditional PSs, CBT-PSs, and PPSs for PLIF and found that neither the operative time nor blood loss was significantly different among them. However, the postoperative drainage volume in the PPS-PLIF group was significantly lower than that in the PS-PLIF and CBT-PLIF groups. Elmekaty *et al*[78] found that CBT-TLIF led to a shorter operative time, less blood loss, and lower CK and C-reactive protein levels than MIS-TLIF and MIS-PLF, while there was no significant difference in functional outcomes among the three techniques. Additionally, the fusion rate was 100% with CBT-TLIF and MIS-TLIF but 90% with MIS-PLF. Screw loosening occurred in 10% of the MIS-PLF group, 7.14% of the MIS-TLIF group and 4.76% of the CBT-TLIF group. Ding *et al*[55] performed a prospective randomized controlled trial study that aimed to compare the results with TLIF using CBT and traditional PSs for treating osteoporosis patients with lumbar degenerative disease. The results indicated similar fusion rates between the two techniques at 6 and 12 mo, while CBT resulted in a significantly lower incidence of screw loosening and better ODIs and JOA scores at 3 mo postoperatively.

Compared with traditional lumbar fusion surgery, the advantages and disadvantages of MIDLF are as follows: Advantages: (1) Strong screw purchase, especially for osteoporosis patients; (2) Minimal invasiveness: The CBT screw is inserted near the middle line in the lumbar posterior approach, and less paravertebral muscle stripping is required. Compared with traditional PS insertion, CBT screw insertion results in less operative blood loss, shorter hospitalization time, lower postoperative CK level, less fat infiltration, and a larger postoperative lumbar dorsal muscle cross-sectional area; (3) Safety: CBT screws are inserted distant from the spinal canal and nerves; and (4) Effectiveness: Combined with various lumbar fusion procedures, CBT can treat a variety of lumbar diseases, lumbar spondylolisthesis, spinal traumas, and infections and produce effective outcomes, especially in the early postoperative period. Disadvantages: (1) It is difficult to place the screw by hand, and the manual feel with the CBT is notably different from that of the traditional pedicle trajectory, which results in a steep learning curve; (2) For patients with thin pedicles, pedicle fracture can easily occur; (3) It is difficult to connect screws and rods when fixing long segments; and (4) Relevant imaging equipment is required to place the screw accurately, and intraoperative fluoroscopy must be performed repeatedly.

MIDLIF is advantageous in the treatment of lumbar spondylolisthesis with osteoporosis due to its superior biomechanics and minimally invasive nail placement. With the maturity and popularization of computer navigation system technology, three dimensional (3D) printing navigation, 3D navigation and robot navigation-assisted CBT screw placement can reduce the complications caused by screw placement errors, address the shortcomings of CBT screw internal fixation technology, and increase the effectiveness of CBT screw internal fixation technology in the treatment of spinal surgical diseases.

ADVANTAGES OF MIDLF IN SPINAL REVISION SURGERY

With the application of posterior lumbar interbody fusion, ASDs caused by fusion have become increasingly prominent, with 5%-16% and 10%-26% of patients with symptomatic ASDs requiring revision surgery 5 and 10 years after lumbar posterior interbody fusion, respectively[79-81]. Compared with the first surgery, revision surgery is more difficult due to the obstruction of the PSs and the influence of surgical scars. The risk of dural sac tears and other complications during revision surgery are increased 1.7 times, and the bleeding volume is increased by 16% in traditional posterior fusion surgery fixed by vertebral arch screws[82,83]. MIDLIF can be used to perform decompression, fusion and fixation on the basis of less soft tissue dissection while retaining the original PSs, providing a new option for posterior revision of ASD.

In revision surgeries, CBT screws can be placed without removing the original PS so that one PS and one CBT screw can be accommodated in the same segment at the same time[84]. In addition, the insertion point of the CBT screw is closer to the midline near the isthmus; it is not necessary to expose the outer edge of the articular process when placing the screw, significantly reducing surgical trauma and bleeding.

Zhang *et al*[85] performed a human cadaveric biomechanical study and found that both CBT screws and PSs can be applied in a revision operation to salvage each other. The biomechanical stability of the traditional PS in revision with CBT is equivalent to that of the original PS, while the stability of the CBT screw in revision with a traditional PS is significantly lower than that of the original CBT screw. The original PS has a great influence on the modified CBT screw; however, the original CBT screw has little influence on the traditional pedicle revision screw[25]. He *et al*[63] used MIDLF with 3D-printed navigation templates in revision surgery to treat ASDs and obtained good clinical efficacy with a short operation duration and little blood loss. Recently, Wang *et al*[86] found that CBT screws were feasible for bridging fixation in ASD revision surgery. Melikian *et al*[87] published a case report on unilateral cortical trajectory screw instrumentation, allowing for posterior instrumentation without having to remove the existing PSs in the setting of ASD. Rho *et al*[88] first applied robotic placement of a CBT screw in the same pedicle as a prior traditional PS for ASD.

STUDY ON THE ACCURACY OF COMPUTER NAVIGATION-ASSISTED CBT SCREW PLACEMENT

With the development and progress of computer navigation systems and related equipment, robot navigation technology, 3D-guided plate navigation, and preoperative 3D CT planning trajectory-assisted placement of CBT screws have addressed the lack of accuracy in manual screw placement and improved the accuracy and safety of CBT screw internal fixation technology in spinal surgery.

To better standardize and increase the accuracy of the trajectory, Matsukawa *et al*[36] attempted to improve the perspective during CBT screw surgery using a CT guide, which acts as a "pedicle diagram" similar to a clock; that is, in the left pedicle, the screw starts in the direction of 5 o'clock and is aimed at the direction of 11-12 o'clock, and in the right pedicle, the starting point is located in the direction of 7 o'clock, and the screw is aimed at the direction of 12-1 o'clock. The authors also believed that the starting point of the sacral CBT screw should be located at the junction of the center of the S1 upper articular process and approximately 3 mm below the lowest edge of the L5 Lower articular process[89]. In the axial plane, the direction is vertical and forward, and in the sagittal plane, the angle is 30°, and the screw directly penetrates the middle of the sacral endplate. Although penetrating the sacral endplate seems dangerous, it produces more stability against pullout forces and loosening[90]. However, Spirig *et al*[91] did not recommend placing CBT screws that penetrate the lumbar vertebral endplate, as no relevant biomechanical advantage is gained, while the potential risk for iatrogenic injury to structures anterior to the spine is increased.

Intraoperative CT (o-arm) image navigation technology combined with CBT screw fixation technology was first used to treat symptomatic adjacent vertebral diseases by Rodriguez *et al*[84] in 2014; CBT screws were placed again in the pedicle in which traditional PSs had been previously placed. This technique avoids the disadvantage of removing the connecting rod in traditional revision surgery and can reduce the operation time and trauma. Similarly, Kotheranurak *et al*[92] used CT-guided and image-guided unilateral CBT screw fixation to treat L5/S1 intervertebral disc diseases in an anterior approach assisted by endoscopy. The results showed that a variety of minimally invasive combined technologies with the assistance of a navigation system can improve the ease and accuracy of screw placement and reduce the amount of surgical trauma. Larata *et al*[93] used intraoperative cone beam CT to insert 618 CBT screws and showed that the accuracy rate of the overall navigation was as high as 98.3%. Kumar *et al*[94] compared the accuracy and complication rate of CBT screw placement under traditional fluoroscopy and CT navigation during the operation. The results showed that the destruction rate of the medial wall of the pedicle and the incidence of cerebrospinal fluid leakage and postoperative infection-related complications in the fluoroscopy group were higher than those in the navigation group.

In designing a 3D-printed navigation template, the surgeon first obtains images through preoperative CT scanning and then uses computer-aided, preset nail tracks to transfer the data to the 3D printer to create an individualized and accurate nail placement navigation template that allows CBT screws to be accurately placed during the operation. First, this technique was limited to cadaveric research[95-96]. Recently, some researchers have used this technique in clinical surgery. Kim *et al*[97] used this technique to treat an L4 spondylolisthesis patient, and the postoperative recovery was satisfactory without any related complications. Marengo *et al*[98] also used this technique to treat 11 patients in the same year. The results showed that the average deviation between the actual position of the screw and the postoperative position was 0.91 mm, and 85.2% of the screw deviation angles were < 2°. Mastsukawa *et al*[99] found that the accuracy rate of the 3D-printed template reached up to 97.5%, and the screw size used in this study was as large as 6.0 mm × 40 mm, which potentially increases the fixation strength. Similarly, Maruo *et al*[100] studied the accuracy of CBT screw placement by surgeons without free-hand experience using 3D-printed navigation template technology. The results showed that the overall accuracy was 91%, which increased to 97% after 10 operations.

Compared with traditional CT navigation technology, robots can avoid the interference of personnel and human errors caused by fatigue and emotion. Le *et al*[101] compared the accuracy of CBT screw placement under robot assistance and traditional fluoroscopy assistance. According to the improved Gertzbein-Robbins classification, the accuracy of the robot-assisted group was as high as 87.2%, while the accuracy of the traditional fluoroscopy-assisted group was only 66.9%. However, the operation time, blood loss and cumulative radiation time were greater than those in the traditional fluoroscopy-assisted group. Le *et al*[101] also found that the use of robots could reduce the rate of facet joint invasion and concluded that a measurement ≥ 45° was a significant risk factor for facet joint invasion in both groups. Khan *et al*[102] compared the accuracy of CBT screw placement assisted by the Mazor X robot and intraoperative 3D CT navigation technology[102]. The results showed that 92 screws in the robot group and 69 screws in the CT group were accurately placed, but there was no significant difference in operation time or bleeding volume.

CONCLUSION

CBT is a technique that can enhance the stability of screw fixation of osteoporotic vertebral bodies without the use of additional materials. It provides a new selection for lumbar internal fixation, especially for osteoporosis and revision cases. According to the anatomical characteristics of the resulting screw channels, the exposure range of the CBT technique is small and provides a safe passage distant from the nerve root and facet joint, which reduces the potential risk of neurovascular and facet joint injury and the incidence of ASDs and can also achieve a minimally invasive effect. Additionally, the CBT screw technique can be used in conjunction with the traditional PS technique and is expected to play an increasingly important role in treating lumbar diseases.

At present, large-scale, high-quality randomized controlled trials on CBT and traditional trajectory technology in lumbar degenerative diseases are being carried out[103,104], and more evidence-based medical evidence will be produced. Of course, with further basic research and clinical practice, clinicians and researchers will achieve a deeper understanding of the CBT technique. In short, the application prospects of CBT technology are worth considering.

FOOTNOTES

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REVIEW

Allogeneic stem cell transplantation in the treatment of acute myeloid leukemia: An overview of obstacles and opportunities

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Abstract

As an important treatment for acute myeloid leukemia, allogeneic hematopoietic stem cell transplantation (allo-HSCT) plays an important role in reducing relapse and improving long-term survival. With rapid advancements in basic research in molecular biology and immunology and with deepening understanding of the biological characteristics of hematopoietic stem cells, allo-HSCT has been widely applied in clinical practice. During allo-HSCT, preconditioning, the donor, and the source of stem cells can be tailored to the patient's conditions, greatly broadening the indications for HSCT, with clear survival benefits. However, the risks associated with allo-HSCT remain high, *i.e.* hematopoietic reconstitution failure, delayed immune reconstitution, graft-versus-host disease, and post-transplant relapse, which are bottlenecks for further improvements in allo-HSCT efficacy and have become hot topics in the field of HSCT. Other bottlenecks recognized in the current treatment of individuals diagnosed with acute myeloid leukemia and subjected to allo-HSCT include the selection of the most appropriate conditioning regimen and post-transplantation management. In this paper, we reviewed the progress of relevant research regarding these aspects.

Key Words: Hematopoietic stem cell; Transplantation; Allogeneic hematopoietic stem cell

transplantation; Leukemia; Treatment

Core Tip: Allogeneic stem cell transplantation remains an important player in the therapeutic armamentarium of acute myeloid leukemia. However, this procedure has its advantages and disadvantages. In this narrative review, we explore the obstacles and opportunities of allogeneic stem cell transplantation in acute myeloid leukemia as well as the recent advances in the field.

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INTRODUCTION

Leukemia is a malignant disease caused by the abnormal proliferation and differentiation of hematopoietic stem cells (HSCs). Chemotherapy is still one of the main treatments for leukemia, with most patients achieving complete remission (CR) after induction and consolidation chemotherapy. However, some patients relapse after months or years despite CR followed by maintenance chemotherapy. To improve the prognosis of leukemia subjects, some researchers have tried to increase the dose of induction and consolidation chemotherapy to kill as many leukemia cells as possible before they become resistant to certain antineoplastic drugs. The results, however, are unsatisfactory. Certain malignant cells, such as leukemic stem cells (LSCs), hide in the bone marrow (BM) niche, resulting in minimal residual disease (MRD), which is difficult to clear and is an important cause of resistance and relapse[1]. In addition, high-dose chemotherapy drugs can easily damage HSCs and cause BM suppression[2-5]. Therefore, an appropriate post-CR treatment plan is important for improving the disease-free survival of leukemia patients.

Hematopoietic stem cell transplantation (HSCT) has been one of the most important breakthroughs in the therapy of malignant tumors over the last five decades. In 1957, Professor Thomas, a renowned hematologist, first used allogeneic BM transplantation to successfully treat hematological malignancies. Since then, allogeneic (allo)-HSCT technology has been improving and has been implemented worldwide. Allo-HSCT has completely transformed the treatment of hematological malignancies, with substantial survival benefits *via* the graft-versus-leukemia (GVL) effect. However, the risks of allo-HSCT include hematopoietic reconstitution failure, delayed immune reconstitution, graft-versus-host disease (GVHD), and post-transplant relapse, which are past and current challenges and research topics in the field of HSCT[1-5].

According to the most recent guidelines of the National Comprehensive Cancer Network, allo-HSCT can be considered in patients diagnosed with acute myeloid leukemia (AML) in the following clinical contexts[6]: Subjects aged less than 60 years who display induction failure after induction with high-dose cytarabine, *i.e.* after at least two courses of intensive induction therapy, and the patient does not achieve complete response or complete response with incomplete hematological recovery; in the setting of post-induction therapy in subjects aged 60 years or more who achieve complete response after induction with standard dose cytarabine and are fit to be subjected to conventional consolidation or in those individuals who display induction failure in whom allo-HSCT preferably should be performed in the setting of a clinical trial; in the setting of post-induction therapy in subjects aged 60 years or more who achieve response after being subjected to lower-intensity regimens; and in patients with relapsed AML after the use of targeted therapy or chemotherapy, depending on the genomic profile of the malignancy.

HEMATOPOIETIC RECONSTITUTION AFTER BONE MARROW TRANSPLANTATION

During allo-HSCT, whether the transplanted donor hematopoietic stem and progenitor cells (HSPCs) can successfully home to the BM niche, with successful hematopoietic reconstitution in an appropriate hematopoietic microenvironment, is key for the success of allo-HSCT. HSPC homing and engraftment is a complex multistep process that involves complex interactions between HSPCs and a range of stromal cells in the hematopoietic microenvironment as well as various molecules, *e.g.*, adhesion molecules and chemokines[7,8].

Primitive $CD34^+$ HSPCs express a wide range of cell adhesion molecules, some of which are closely related to HSPC homing, *e.g.*, P-selectin glycoprotein ligand 1, integrins such as very late antigen-4, lymphocyte Peyer's patch adhesion molecule-1, lymphocyte function-associated antigen-1, specific antigens such as CD44, and cadherins[7,9]. Most of the adhesion molecules on HSPCs have corresponding ligands on the BM mesenchymal stromal cells (MSCs) and the extracellular matrix. The adhesion molecules and their ligands recognize each other and mediate the adhesion of HSPCs (Table 1).

Upon entering the BM cavity from the blood circulation, the initial adherence of HSPCs to the BM sinusoidal endothelial cells requires P-selectin glycoprotein ligand 1, P-selectin, and E-selectin[10]. After this, the adhesion between HSPCs and BM sinusoidal endothelial cells becomes tighter, and the HSPCs enter the BM hematopoietic microenvironment by passing through BM sinusoidal endothelial cells. The process requires integrins and immunoglobulin (Ig) superfamily members, especially the very late antigen-4/vascular cell adhesion molecule-1 and lymphocyte function-associated antigen-1/intercellular adhesion molecule-1 pathways[7,11]. In the BM hematopoietic microenvironment, HSPCs adhere and interact with stromal cells and the extracellular matrix and stimulate BM stromal cells to secrete hematopoietic cytokines to regulate the quiescence, self-renewal, proliferation, and differentiation of HSPCs[12-30].

A large body of evidence indicates that the axis composed of stromal derived factor-1 (SDF-1/CXCL12) secreted by osteoblasts and endothelial cells and the HSC surface receptor CXCR4 plays a critical role in HSC homing and subsequent engraftment. The SDF-1/CXCR4 signal induces HSPCs to pass through the endothelial layer to adhere to the BM matrix, promoting HSPC homing and engraftment *via* chemotaxis and participating in the regulation of HSPC survival and proliferation[7,31]. Given the important role of SDF-1/CXCR4 in HSPC homing and engraftment, the regulation of this signal axis is also important for promoting post-transplant hematopoietic reconstitution. Studies have shown that mild heat treatment, prostaglandin E2, histone deacetylase inhibitors, and hypoxia inducible factor-1α enhance the SDF-1/CXCR4 signal and promote HSPC homing and engraftment[11]. In addition to the SDF-1/CXCR4 axis, other chemokine axes and numerous molecules, *e.g.*, receptor tyrosine kinase, thrombopoietin, and matrix metalloproteinases, are involved in HSPC maintenance, homing, and engraftment[23,25,32,33] (Table 1).

Recent research has delineated that the adhesion molecule connexin-43 plays an important role in BM regeneration and HSPC engraftment after irradiation preconditioning. With connexin-43-mediated cell-to-cell contact, donor HSPCs transfer mitochondria to postradiation recipient MSCs, promoting the metabolic recovery of radiation-damaged MSCs and improving the BM hematopoietic compartment reconstitution and donor HSPC engraftment[22]. The mechanism of HSPC homing and engraftment is depicted in Figure 1.

MSCs are the main components of the BM hematopoietic microenvironment and play important roles in supporting, regulating, and protecting HSPCs[34,35]. During HSCT preconditioning, chemotherapy/radiotherapy causes damage to MSCs, resulting in severely low numbers of MSCs, impaired cytokine production and adhesion molecule expression, and impaired function in supporting and regulating hematopoiesis[36].

Histocompatibility is another consideration for allogeneic transplantation, as transplantation failure may also occur not only due to immune rejection but also to major histocompatibility complex (MHC) restriction between donor HSCs and recipient stromal cells and because recipient stromal cells do not support the proliferation and differentiation of donor HSCs. There is a complex interplay between MSCs and HSCs in HSCT, as MSCs are known to support HSCs and enhance their engraftment. Due to their properties, *i.e.* adherence to plastic and ability to be expanded *ex vivo* as well as the lack of reported side effects after their administration, MSCs have been employed in clinical patient research, and MSC infusion has been co-administered with HSCs to enhance the engraftment of the latter, particularly in the setting of haploidentical allo-HSCT with/without T cell depletion. In addition, MSCs secrete soluble molecules (*e.g.*, interferon (IFN)-γ, cytokines, chemokines, *etc.*) and exhibit immunomodulatory actions, having already been employed successfully in the prevention and treatment of GVHD in individuals who had been subjected to allo-HSCT.

Several of the processes in which MSCs are involved include a decrease in inflammation and in the proliferation of B cells and T cells as well as an increase in tissue repair[34,37,38]. *In vitro* cell culture studies have demonstrated that when primed with nitric oxide MSCs can significantly boost the engraftment potential of HSCs *via* the intercellular transfer of microvesicles harboring mRNAs encoding HSC-supportive genes[39]. *In vitro* research has revealed that, under mild hypoxia (5% oxygen), MSCs promote CXCR4 expression in $CD34^+CD38^-$ cells, thereby enhancing HSPC homing[40].

MSCs were investigated in phase I/II clinical trials of HSCT to promote HSC engraftment. In clinical applications, MSCs have been used to expand HSCs *in vitro*[34]. Previous assessments have reported that the engraftment success rate is related to several factors, *e.g.*, the number of stem cells, the stem cell source, donor-specific anti-human leukocyte antigen (HLA) antibodies (DSAs), and the pretreatment protocol. In most cases, increasing the HSPC infusion dose contributes to successful HSPC engraftment and hematopoietic reconstitution. In addition, the quantity and quality of the grafts, as well as the age of donor, can also affect immune reconstruction after allo-HSCT. For example, allo-HSCT from donors aged > 50 years has been linked with lower CD8+CD45RA+ naïve T cell and CD19+ B cell counts,

Table 1 Molecules that mediate hematopoietic stem and progenitor cell adhesion and chemotaxis during transplantation

HSPC receptor	Bone marrow ligands	Effect	Ref.
PSGL-1/CD162	Selectins (P and E)	Promote HSPC homing	[10]
β_1 integrin	Opn	Contribute to HSC trans-marrow migration toward the endosteal region	[17,18]
VLA-4/$\alpha_4\beta_1$	VCAM-1, fibronectin	Promote HSPC homing	[7,11]
VLA-5/$\alpha_5\beta_1$	Fibronectin	Promote HSPC homing and proliferation	[19,20]
LFA-1/$\alpha_L\beta_2$	ICAM-1	Promote HSPC homing	[7,11]
LPAM-1/$\alpha_4\beta_7$	MAdCAM-1	Promote HSPC homing and engraftment	[21]
Cx43		Participate in the formation of intercellular transmembrane channels, facilitate the transportation of mitochondria or other substances, and promote bone marrow regeneration and HSPC engraftment	[22]
CXCR4	SDF-1	Promote HSPC homing and engraftment and participate in the regulation of HSPC survival and proliferation	[7]
c-kit	SCF	The transmembrane isoform of SCF is critical in the lodgment and detainment of HSCs within the bone marrow niche	[23]
c-MPL	TPO	TPO promotes the survival and proliferation of HSPCs and upregulates SDF-1 in the bone marrow niche, thereby contributing to HSPC homing and engraftment	[24,25]
CD44/Pgp-1	Selectins (P, E and L), HA	CD44 and HA play a key role in SDF-1-dependent transendothelial migration of HSPCs and their final anchorage within the bone marrow niche	[26]
CD82/KAI1		CD82 modulates HSPC bone marrow maintenance, homing, and engraftment	[27]
Anxa2r	Annexin II/Anxa2	Regulate stem cell adhesion, homing, and engraftment	[28]
CaR	Ca^{2+}	Enhance HSC lodgment and engraftment in the bone marrow niche	[29]
N-cadherin	N-cadherin	N-cadherin-mediated cell adhesion is functionally required for the establishment of hematopoiesis in the bone marrow niche after bone marrow transplantation	[30]

Anxa2r: Annexin II receptor; c-kit: Tyrosine-protein kinase kit; c-MPL: Thrombopoietin receptor; Ca^{2+}: Calcium; CaR: Calcium-sensing receptor; CD162: cluster of differentiation 162; CD44: Cluster of differentiation 44; CD82: Cluster of differentiation 82; Cx43: Connexin 43; CXCR4: C-X-C chemokine receptor 4; HA: Hyaluronic acid; HSC: Hematopoietic stem cell; HSPC: Hematopoietic stem and progenitor cells; ICAM-1: Intercellular adhesion molecule 1; KAI1: Kangai 1; LFA-1: Lymphocyte function-associated antigen-1; LPAM-1: Lymphocyte Peyer's patch adhesion molecule-1; MAdCAM-1: Mucosal addressin cell adhesion molecule-1; MPL: Myeloproliferative leukemia gene; Opn: Osteopontin; Pgp-1: Phagocytic glycoprotein-1; PSGL-1: P-selectin glycoprotein ligand-1; Ref.: Reference; SCF: Stem cell factor; SDF-1: Stromal cell-derived factor-1; TPO: Thrombopoietin; VCAM-1: Vascular cellular adhesion molecule-1; VLA-4: Very late antigen 4; VLA-5: Very late antigen 5.

reduced serum IgM and IgA concentrations, and higher Epstein-Barr virus reactivation rates[12,41-45].

However, it should be noted that for allogeneic peripheral blood stem cell transplantation (allo-PBSCT), a high dose of $CD34^+$ cells increases the risk of extensive chronic graft-versus-host disease (cGVHD)[46]. The higher incidence of extensive cGVHD leads to adverse effects on the patient's prognosis and increases transplant-related mortality, particularly among subjects receiving T cell depleted allogeneic transplantation with myeloablative conditioning. In contrast, individuals who are subjected to low-intensity preconditioning rather than myeloablative regimens may benefit from a higher dose of $CD34^+$ cells, as it has been shown that relapse and/or progression rates were significantly lower (9% *vs* 36%) in subjects who had received an elevated number of $CD34^+$ cells[46]. Most clinical studies have indicated that in HLA-identical sibling donor transplantation, the application of peripheral blood-derived stem cells accelerates platelet and neutrophil engraftment, which is related to the use of G-CSF during mobilization of peripheral blood-derived stem cells[47-49]. In addition to successfully mobilizing $CD34^+$ stem cells from the BM of healthy donors, G-CSF can induce changes in immune cell function, redirect T cell polarization, and change the expression of adhesive molecules, resulting in rapid and long-lasting engraftment[50].

With the widespread development of HLA haploidentical stem cell transplantation in recent years, engraftment failure and poor engraftment are still an urgent problem to be solved in HLA haploidentical transplantation. DSAs are the most important factors causing engraftment failures of HLA

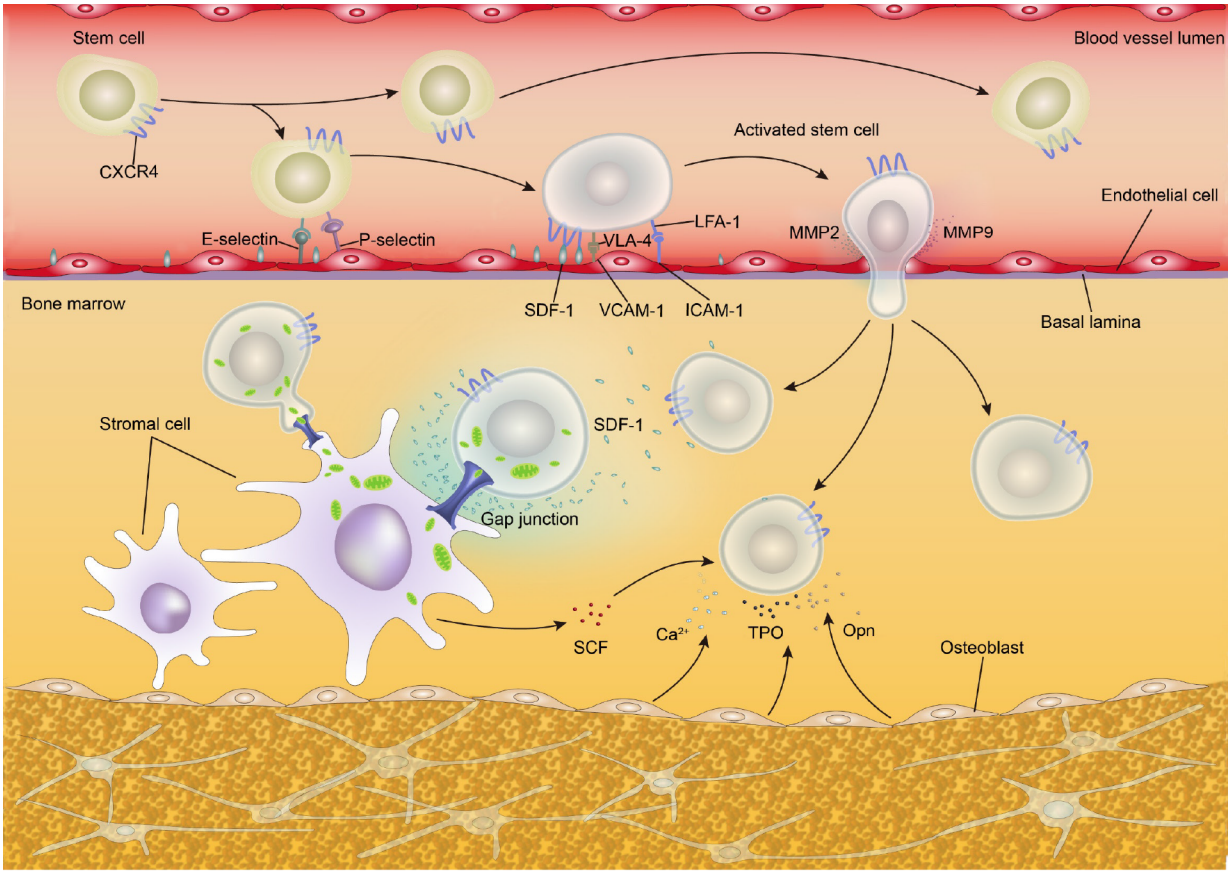

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Figure 1 Mechanism underlying hematopoietic stem and progenitor cells homing and engraftment. Numerous adhesion molecules and chemokines are involved in the regulation of hematopoietic stem and progenitor cells (HSPCs) homing and engraftment. The interaction between recipient bone marrow stromal cells and donor HSPCs contributes to HSPC homing and engraftment. In addition, donor HSPCs improve the metabolism of recipient bone marrow stromal cells *via* mitochondrial transfer, accelerating the recovery of damaged bone marrow stromal cells. Ca^{2+}: Calcium; CXCR4: C-X-C chemokine receptor 4; ICAM-1: Intercellular adhesion molecule-1; LFA-1: Lymphocyte function-associated antigen-1; MMP-2: Matrix metalloproteinase 2; MMP-9: Matrix metalloproteinase 9; Opn: Osteopontin; SCF: Stem cell factor; SDF-1: Stromal derived factor-1; TPO: Thrombopoietin; VCAM-1: Vascular cell adhesion molecule-1; VLA-4: Very late antigen 4.

haploidentical transplantation. Chang *et al*[51] suggested that high DSA levels were associated with primary engraftment failure and poor primary engraftment in HLA haploidentical transplantation. Ciurea *et al*[52] used plasma exchange, rituximab, intravenous immunoglobulins, and irradiated donor buffy coat to intervene in patients with high DSA levels and found that the engraftment success rate was higher in patients with decreased DSAs and negative complement component 1q. Pretreatment protocols can also affect the engraftment success rate. The Beijing Protocol and the post-transplant cyclophosphamide protocol are some of the most commonly used pretreatment protocols for HLA haploidentical transplantation worldwide. Recently, Tang *et al*[53] conducted a retrospective study and found that the Beijing Protocol exhibited some advantages *vs* single-cell source + the post-transplant cyclophosphamide transplant regimens in terms of 30-d neutrophil engraftment rate, 90-d platelet engraftment rate, median neutrophil engraftment time, and platelet engraftment time. Other pretreatment protocols have been previously summarized by Baumeister *et al*[54] elsewhere.

In recent years, researchers have paid more attention to alternative routes of stem cell administration to reduce the ineffective homing of donor cells[55,56]. Animal model studies have highlighted that compared with intravenous infusion, intra-bone marrow injections for HSPC transplantation are more effective in promoting hematopoietic reconstitution and reducing the incidence of GVHD[57-59]. At present, the clinical application of intra-bone marrow injections is still in its infancy and is mostly used for umbilical cord blood cell transplantation.

POST-TRANSPLANT IMMUNE RECONSTITUTION

HSCs have the capacity for self-renewal, to proliferate, and to differentiate into hematopoietic cells and immune cells. Therefore, HSCT is essentially a dual transplantation of hematopoietic cells and immune cells. After allo-HSCT, the recipient's hematopoietic system and immune system are reconstituted

simultaneously. The restoration of immune function helps patients fight pathogens and ensures successful HSCT. For allo-HSCT recipients, immune reconstitution is a highly dynamic process, including the innate immune system reconstitution and adaptive immune system reconstitution. Post-transplant immune reconstitution takes time, and different immune cells follow different reconstitution patterns, having important implications for the outcome of allo-HSCT.

The innate immune system is mainly composed of natural killer (NK) cells, neutrophils, monocytes, macrophages, and antigen presenting cells (APCs)[60], of which NK cells are the first group of lymphocytes to recover after transplantation, taking only 1-4 mo to return to normal levels, independent of the stem cells source[61-64]. The function of NK cells is regulated by the interaction between killer immunoglobulin-like receptors and the ligand HLA[65]. For haploidentical transplantation, HSCTs with alloreactive donor NK cells (killer immunoglobulin-like receptor-HLA mismatched HCT) are shown to be associated with less relapse and better overall survival[66-69]. Such alloreactive NK cells may also have a beneficial effect on alleviating GVHD because they can eliminate host APCs that prime alloreactive T cells that cause GVHD[67,70,71]. As with NK cells, neutrophils and monocytes also recover in a short period of time after transplantation. Dendritic cells (DCs), shown to be the most potent APC, take longer to recover. In adults, while donor DCs can be detected in the peripheral blood in the first few weeks after stem cell transplantation, the total number may not return to normal even after a year[60,72,73]. Furthermore, previous investigations have pinpointed that while peripheral blood DCs are mainly derived from donors (> 80% by day 14), up to 70% of tissue DCs may still come from the host[60,74-76]. These tissue DCs of host origin may persist for up to a year following HSCT[75]. Researchers have confirmed that host APCs, rather than donor APCs, play an important role in the post-allo-HSCT GVL effect and GVHD[77-79]. Therefore, proper regulation of host APCs may alleviate GVHD and enhance the GVL effect.

Adaptive immune reconstitution mainly includes the restoration of the number and function of B cells and T cells. Reconstitution of the B cell compartment after HSCT occurs primarily through *de novo* regeneration from BM progenitors[80]. Generally, the proportion of total B cells in most patients reaches normal levels by 3 mo, but the absolute number may not return to normal for 6-12 mo[81-83]. During the 1st year of HSCT, most reconstituted B cells are mainly composed of transitional and naive subsets. However, the restoration of memory B cells takes much longer[83]. Consistent with this, IgM levels recover in 2 to 6 mo after transplantation, and then IgG levels return to close to normal in 3 to 18 mo after transplantation, whereas IgA reconstitution may be delayed for up to 3 years[60].

T cell immune reconstitution is markedly different from B cell immune reconstitution. T cells mainly include two subgroups, CD4$^+$ T cells and CD8$^+$ T cells, which are reconstituted through thymus-independent and thymus-dependent pathways. The early increase in blood T lymphocyte numbers is related to the thymus-independent peripheral expansion of mature donor T cells. The recovery of a broader T cell repertoire depends on the *de novo* generation of naïve T cells through the thymus after the engraftment and differentiation of hematopoietic stem cells in the BM[80,84]. Preconditioning or GVHD impairs thymus function, resulting in decreased CD4$^+$ T cells after transplantation. Memory or effector CD8$^+$ T cells can rapidly expand through a thymus-independent pathway and return to normal in 12 mo. Therefore, an inverted CD4:CD8 ratio after transplantation is one of the earliest signs of T cell reconstitution and may last for several years, depending on preconditioning and GVHD prevention regimens[83].

CD4$^+$ CD25$^+$ regulatory T cells (Tregs), a subgroup of CD4$^+$ T-cells, play an important role in HSCs maintenance. Cytotoxic T-= cell activation and decreased Treg counts are believed to be the etiology of idiopathic severe aplastic anemia[85]. Tregs reconstitute faster than effector T cells after HSCT. They suppress the activation and proliferation of effector T cells and downregulate the body's response to foreign antigens or autoantigens, thereby maintaining immune tolerance[86]. Numerous recent studies show that an imbalance between Tregs and effector T cells may be an important link in the occurrence of GVHD[87,88].

Post-transplant immune reconstitution is affected by many factors, such as the intensity of preconditioning, recipient thymus function, recipient age, graft source, and GVHD (Table 2). Delayed immune reconstitution makes HSCT recipients susceptible to various infections. In fact, despite the use of routine peritransplant prophylactic antibiotics, approximately 80%-85% of HSCT recipients contract infections, which is one of the leading causes of nonrelapse death after allo-HSCT[89]. At present, there is no "standard-of-care" approach to enhance post-transplant immune reconstitution. However, several strategies such as protecting the thymic epithelium, stimulating thymopoiesis, or increasing the number of T lymphoid precursors, are being investigated in preclinical models as well as early clinical trials[83]. The effectiveness of these measures remains to be further verified and improved in practice.

Several studies show that immune reconstitution, especially the reconstitution of CD4$^+$ T cells, is inversely related to age. However, some studies report that age has no effect on the reconstitution of any subgroup of lymphocytes[63,90,91].

Graft source

Immune reconstitution occurs faster after PBSCT than after BMT. This may be because PBSCT grafts are rich in mature lymphocytes. Delayed immune reconstitution after umbilical cord blood cell transplantation is related to low lymphocyte count and immature immune cells in umbilical cord blood

Table 2 Main factors for post-transplant immune reconstitution

Factors	Effect	Ref.
Recipient age	Several studies show that immune reconstitution, especially the reconstitution of $CD4^+$ T cells, is inversely related to age. However, some studies report that age has no effect on the reconstitution of any subgroup of lymphocytes	[63,90,91]
Graft source	Immune reconstitution occurs faster after PBSCT than after BMT. This may be because PBSCT grafts are rich in mature lymphocytes. Delayed immune reconstitution after UCBT is related to low lymphocyte count and immature immune cells in umbilical cord blood	[61,92-95]
HLA matching between donor and recipient	HLA mismatch causes delayed reconstitution of neutrophils and T cells	
Intensity of preconditioning	Several studies show that compared with MA-SCT, RICSCT reduces thymus damage and promotes immune reconstitution. However, some studies show no significant difference in recipient immune reconstitution between these two transplantation methods	[60,96-98]
GVHD	GVHD damages thymus structure and function and interferes with T cell differentiation at all stages, thereby affecting T cell reconstitution. GVHD also affects the recovery of B cell number and function	[84,99]
GVHD prevention	Donor TCD reduces the risk of GVHD; however, the lack of T cells increases the risk of infection and delayed immune reconstitution	[100]
	The use of ATG or alemtuzumab has a negative effect on the reconstitution of T cells and B cells	[101-103]

ATG: Antithymocyte globulin; BMT: Bone marrow transplantation; CD4: Cluster of differentiation 4; GVHD: Graft-versus-host disease; HLA: Human leukocyte antigen; MA-SCT: Myeloablative stem cell transplantation; PBSCT: Peripheral blood stem cell transplantation; Ref.: Reference; RICSCT: Reduced-intensity conditioning stem cell transplantation; TCD: T cell depletion; UCBT: Umbilical cord blood stem cell transplantation.

[61,92-95].

HLA matching between donor and recipient

HLA mismatch causes delayed reconstitution of neutrophils and T cells.

Intensity of preconditioning

Several studies show that compared with myeloablative stem cell transplantation, reduced-intensity conditioning stem cell transplantation reduces thymus damage and promotes immune reconstitution. However, some studies show no significant difference in recipient immune reconstitution between these two transplantation methods[60,96-98].

GVHD

GVHD damages thymus structure and function and interferes with T cell differentiation at all stages, thereby affecting T cell reconstitution. GVHD also affects the recovery of B cell number and function[84,99].

GVHD prevention

Donor T cell depletion reduces the risk of GVHD; however, the lack of T cells increases the risk of infection and delayed immune reconstitution[100]. The use of antithymocyte globulin (ATG) or alemtuzumab has a negative effect on the reconstitution of T cells and B cells[101-103].

REGULATION OF GVL AND GVHD

For allo-HSCT, an important mechanism for the treatment of leukemia is that donor immune cells recognize the surface antigens of recipient leukemia cells and trigger an immune response to attack and clear any residual leukemia cells, which is known as the GVL effect. GVL effect is closely related to GVHD, as both have similar pathways, effector cells, and cytokines. Therefore, during immune reconstitution after allo-HSCT, the precise regulation of GVL and GVHD (*i.e.* suppressing GVHD while preserving GVL) plays an important role in the final outcome of allo-HSCT[104,105].

The mechanism of action of GVHD and GVL is very complex and not entirely clear. The interactions between many donor and recipient cells and cytokines make the mechanism even more challenging to understand. It is believed that donor T cells play an important role in the occurrence of GVHD and GVL. Acute GVHD (aGVHD) has three pathophysiological stages: (1) Activation of APCs by the underlying disease and the HCT conditioning regimen. The damaged host tissue produces a large amount of proinflammatory cytokines, *e.g.*, tumor necrosis factor alpha (TNF-α) and chemokines, with elevated expression of adhesion molecules, MHC antigens, and costimulators on host APCs; (2) Donor T

cell activation. Donor T cells proliferate and differentiate in response to host APCs. Activated donor T cells secrete a large amount of Th1 cytokines, such as IFN-γ, interleukin (IL)-2, and TNF-α, which trigger aGVHD; and (3) Cellular and inflammatory effector phase. The complex cascade of cytotoxic T lymphocytes, NK cells, and soluble inflammatory mediators (*e.g.*, TNF-α, IFN-γ, and IL-1) produces synergistic effects and causes further local tissue injury, inflammation, and target tissue damage[106].

The pathophysiology of cGVHD differs from that of aGVHD and is believed to be related to the following factors: (1) Thymus damage and defective negative selection of T-cells, promoting the production of autoreactive T cells; (2) Decreased $CD4^+CD25^+$ Tregs, affecting the suppressive effect of Tregs on effector T cells; (3) Abnormal activation of B cells, promoting the production of autoantibodies and subsequently an autoimmune response; and (4) The formation of profibrotic lesions[107].

GVHD-related tissue damage, as well as GVL-linked tumor elimination, seem to share common immunological mechanisms[108]. Based on this understanding, mitigating the risk of GVHD while maximizing the GVL effect seems to be unrealistic. Clinically, clearing donor T cells effectively reduces the occurrence of and damage by GVHD; however, this approach also weakens the GVL effect, which results in a much higher risk of recurrent leukemia, especially chronic myeloid leukemia. For recurrent cases, donor lymphocyte infusion (DLI) (containing primarily T cells) enables long-term remission[109, 110]. These data indicate that GVHD and the GVL effect are interdependent and that both are T cell dependent. However, recent studies show that GVHD and the GVL effect may be mediated by different subgroups of T cells. In the peripheral blood, the αβ T cell receptor is expressed by 95% of T cells, whereas the γδ T cell receptor is expressed by the remaining T cells. Since the primary mediators in GVHD are alloreactive αβ T cells, their depletion from the graft is expected to decrease the chances of GVHD development. In contrast, γδ T cell receptor-expressing lymphocytes exert anti-infectious and anti-leukemia actions, are not marked by alloreactivity, and are not involved in GVHD occurrence. Notwithstanding, the interest towards the use of γδ T cells in allo-HSCT has increased and are currently under investigation by the international scientific community[111-115].

Allo-HSCT studies in mice show that naïve T cells consistently cause severe GVHD, whereas memory T cells cause milder or no GVHD and have critical graft-versus-tumor functions[116-118]. Subsequent clinical trials have confirmed that the removal of donor naïve T cells effectively reduces the incidence of GVHD and opportunistic infections, without any significant increase in relapse[118-120]. In addition, GVL and GVHD effector T cells have different target antigens. For GVHD effector T cells, the target antigens are MHC antigens and minor histocompatibility antigens (MiHAs); for GVL effector T cells, the target antigens are mainly MiHAs on recipient leukemia cells. Therefore, hematopoietic system-specific MiHAs expressed on leukemic cells are considered important targets for leukemia-specific cellular immunotherapy with a low risk of GVHD[121].

Cytokines are critical drivers of both GVHD and GVL, and current evidence indicates that different cytokines may play different roles in GVHD *vs* the GVL effect[122-133]. In a recent study, Tugues *et al* [108] used an MHC-mismatched HSCT mouse model and found that donor T cell-derived granulocyte-macrophage colony-stimulating factor (GM-CSF) can drive GVHD pathology by licensing donor-derived phagocytes to produce inflammatory mediators such as IL-1 and reactive oxygen species (ROS). Moreover, anti-GM-CSF treatment improved the survival of recipient mice without affecting the GVL effect of alloreactive T cells, suggesting that GM-CSF may be an important target for GVHD-GVL uncoupling. These data indicate that GVHD and the GVL effect are somewhat independent of each other and are not completely parallel, which makes it possible to target GVHD and the GVL effect separately in allo-HSCT recipients. In addition, alloreactive NK cells seem to play a role in the GVL effect especially in the early period that follows the execution of allo-HSCT (*via* interaction in the BM of the recipient between the donor HLA environment and the reconstitution of NK cells) without being involved in the development of GVHD[68].

To improve allo-HSCT efficacy and safety, researchers are making great progress in separating GVHD and the GVL effect, including the early prediction of GVHD risk, the modification of donor graft cells, and drug interventions (Table 3). However, the outcomes in clinical practice are still unsatisfactory. An important reason is an inadequate understanding about the mechanism of action of GVHD and the GVL effect. While it is known that GVHD and the GVL effect may involve different subgroups of T cells, it is challenging to identify these T cells. With the advent and application of new detection methods such as sequencing, a solution may be developed to address this issue. For example, T cell receptor high-throughput sequencing can be used to analyze and identify the entire T cell library involved in GVHD and the GVL effect, thus helping researchers learn more about relevant T cells, clarify the targets and mechanisms of different effector cells, and better separate GVHD and GVL.

MECHANISM OF POST-TRANSPLANT LEUKEMIA RELAPSE

Over the past decades, the transplant-related mortality due to post-transplant complications such as GVHD and infections has decreased due to continuous improvements in stem cell transplantation technology. Post-allo-HSCT relapse has become the major cause of treatment failure and is associated with a dismal prognosis[134]. Post-allo-HSCT relapse may come from normal donor cells, known as

Table 3 Strategies to separate graft-versus-host disease and graft-versus-leukemia

Separation strategies	Approaches	Brief description	Ref.
GVHD risk prediction	GVHD biomarker testing	Contributes to GVHD diagnosis and provides evidence for the early use of anti-GVHD drugs	[123]
	Cytokine gene polymorphism testing	Helps to identify patients with a high risk of severe GVHD and take preventive measures	[124]
Modification of donor graft cells	Donor T cell depletion	Donor T cell depletion reduces GVHD while increasing the risk of infections, graft rejection, and disease relapse	[109]
	Graft-specific cell population depletion	Removing specific cell populations such as naïve T cells in the graft that consistently cause severe GVHD	[118]
	DLI to treat relapse	DLI is very effective in the treatment of relapsed slow-growing hematopoietic malignancies such as CML; however, the mechanism is unknown	[122]
	Application of CAR T cell	The combination of scFv that identifies leukemia-specific antigens and the activating domain of T cells enhances specific identification and killing of leukemia cells	[125,126]
	Suicide gene transduced donor lymphocyte infusion	A genetically modified suicide gene is introduced. Donor lymphocytes expressing this gene are sensitive to prodrugs, a feature that can be used when needed to regulate GVHD through the drug clearance of transduced cells	[127]
	Selecting memory T cells	Memory T cells cause mild or no GVHD and have critical graft-versus-tumor functions	[118]
	Enhancing activated γδ T cells	γδ T cells have the ability to kill leukemic blasts, and allogeneic TCR γδ T cells are not alloreactive and do not cause GVHD	[113]
	Selecting Tregs	Tregs suppress the activation and proliferation of effector T cells and downregulate the body's response to foreign antigens or autoantigens	[86]
	Modifying/selecting other cells in the grafts	Selecting mesenchymal cells, NK cells, and manipulating dendritic cells and dendritic cell subsets	[79,122,129]
Drug intervention	Application of immunosuppressants	Various immunosuppressants suppress T cells and reduce GVHD *via* different mechanisms	[130]
	Application of HDACis	HDACis, such as vorinostat, downregulate inflammatory cytokines and increase the number of Tregs, thereby reducing the occurrence of GVHD, without effecting the GVL effect of donor CTLs	[131,132]
	Suppression of cytokines related to the occurrence of GVHD	Th1 cytokines such as TNF-α, IFN-γ, and IL-6 are related to aGVHD; Th2 cytokines such as IL-4, IL-5, and IL-10 are related to cGVHD. Appropriate regulation of these cytokines facilitates GVHD management	[122]
	Enhancing cytokines that suppress GVHD	Various cytokines such as IL-11 and keratinocyte growth factor reduce GVHD while preserving the GVL effect	[122]
	Targeting MiHAs on hematopoietic cells	CTLs targeting MiHAs such as HA-1 and HA-2 (expressed on hematopoietic cells only) promote the GVL effect	[121]
	Development and application of tumor vaccines	Vaccines targeting MiHAs on hematopoietic cells and leukemia-specific antigens improve GVL specificity	[133]

aGVHD: Acute GVHD; CAR: Chimeric antigen receptor; cGVHD: chronic GVHD; CML: Chronic myeloid leukemia; CTLs: Cytotoxic T lymphocytes; DLI: Donor lymphocyte infusion; GVHD: Graft-versus-host disease; GVL: Graft versus leukemia; HA-1: Histocompatibility antigens 1; HA-2: Histocompatibility antigens 2; HDACis: Histone deacetylase inhibitors; IFN-γ: Interferon-γ; IL-10: Interleukin 10; IL-4: Interleukin 4; IL-5: Interleukin 5; IL-6: Interleukin 6; MiHAs: Minor histocompatibility antigens; NK: Natural killer; Ref.: Reference; scFv: Single-chain variable fragment; TCR: T cell receptor; Th2: T-helper 2; TNF-α: Tumor necrosis factor α; Tregs: Regulatory T cells.

donor cell leukemia (DCL; rare, 0.12% to 5.0%), or recipient cells (most cases)[135,136,137]. Despite the remarkable advancement in allo-HSCT technology in recent years, there has been little progress on how to reduce post-allo-HSCT relapse or improve the survival of relapsed patients. The main reason is a lack of information about the mechanism of post-allo-HSCT relapse.

DCL was first recognized in 1971. Since then, few DCL cases have been reported. The molecular mechanisms involved in DCL occurrence seem to involve cytogenetic abnormalities (chromosome 7 monosomy has been depicted in more than one-fifth of DCL cases) or genetic aberrations that arise in *RUNX1*, *ASXL1*, *DNMT3A*, *IDH1/2*, *EZH2*, *JAK2*, *CEBPA*, *GATA2*, and other genes. In addition, it has been hypothesized that leukemia cells could have been transferred from the donor during the allo-

HSCT procedure. Moreover, several theories support the fact that DCL can arise due to reduced immune surveillance following allo-HSCT, the genomic instability of the donor cells, or an aberrant stromal niche that exhibits a pro-leukemia potential[138,139].

For leukemia relapse derived from recipient cells, researchers had believed that MRD was the root cause of the relapse. However, a growing body of evidence indicates that this theory cannot fully explain the mechanism of leukemia relapse. With advancements in human whole genome sequencing technology, several studies have demonstrated the presence of clonal evolution in leukemia relapse[140-142]. Mullighan *et al*[140] analyzed the genome-wide DNA copy number in the diagnosis and relapse samples of 61 children with acute lymphoblastic leukemia (ALL) and found concordance between the postchemotherapy relapse leukemia clone and the diagnosis clone in only 8% of the patients; in most cases, the relapse leukemia clone evolved from the diagnosis clone or normal ancestral clones. In an analysis of 92 cases of relapsed pediatric ALL, Waanders *et al*[141] found that relapsed leukemic cells propagate primarily from clones already expanded at diagnosis and rarely from unexpanded dormant ancestral clones, suggesting that the information gleaned through subclonal mutation analysis at diagnosis may help to predict relapse risk and select rational therapeutic measures with minimal relapse potential.

In recent years, minor diagnosis subclones that initiate an evolutionary trajectory toward relapse (termed diagnosis relapse initiating clones, dRI) had been identified in both ALL and AML[143,144]. Compared with other diagnosis subclones, dRIs are drug tolerant with distinct engraftment and metabolic properties[143]. Genomic analysis of matched diagnosis and relapse samples showed that relapse often arose from dRIs[143], suggesting that the isolation and identification of dRIs and the elimination of dRIs by targeting the unique metabolic and transcription pathways may be novel approaches to prevent leukemia relapse.

Another important factor for post-allo-HSCT relapse is the immune escape of leukemia cells. With immune escape, some leukemia cells avoid a potent GVL effect after transplantation and hide in the BM niche to form MRD and eventually lead to leukemia relapse. Several studies showed that the loss of HLA on the surface of leukemia cells prevented T cells from recognizing leukemia cells, an important mechanism of immune escape[145,146]. In addition, the changes in the number and function of T cell subsets after allo-HSCT, as well as the high expression of the T cell immune coinhibitory receptors programmed cell death protein 1, cytotoxic T lymphocyte-associated antigen-4, and T cell immunoreceptor with Ig and ITIM domains (TIGIT), are closely related to the immune escape of leukemia cells [147,148]. The mechanism of post-allo-HSCT relapse is very complex and multifactorial, and more extensive and in-depth research is needed to clarify the mechanism.

INTERVENTION AND TREATMENT STRATEGIES FOR POST-ALLO-HSCT RELAPSE

Post-allo-HSCT relapse is a challenging issue for the treatment of leukemia. The overall incidence of post-allo-HSCT relapse is 20% to 30%. For refractory and high-risk leukemia, the relapse rate is 50% or higher[149,150]. Post-transplant relapse has severe impacts on allo-HSCT outcomes because it affects long-term survival and is a major cause of death in leukemia patients after transplantation. Therefore, the identification of the risk factors for post-allo-HSCT relapse and post-transplant indicator monitoring are useful for preventing post-transplant relapse and for the timely identification of early relapse. Furthermore, optimizing treatment strategies with a personalized treatment plan will help to reduce post-transplant relapse and improve survival.

Many factors are related to post-transplant relapse, including disease type, pretransplant disease status, risk stratification, donor source, stem cell source, preconditioning, and GVHD (Table 4). Pretransplant disease status is the most important factor. The risk of relapse is high in nonremission patients and patients with a high level of residual leukemia cells before transplantation[151]. Studies have proven that pre-HSCT MRD may be an independent prognostic factor for relapse in AML patients after receiving myeloablative HSCT. The 2-year overall relapse rate is significantly higher for patients with MRD than for patients without MRD before transplantation (58% *vs* 14%). The 5-year overall survival rate is 26% and 79%, respectively, suggesting that the presence of pretransplant MRD is positively correlated with post-transplant relapse and mortality[151].

Kebriaei *et al*[151] retrospectively analyzed the data of 68 adult patients with AML/myelodysplastic syndrome and found that the transplantation outcome was inversely related to the pretransplant tumor load. The mortality rate due to post-transplant relapse increased 1.21 times for every 10% increase in the percentage of leukemia blasts in the BM before transplantation. These findings suggest that reducing the pretransplant tumor burden and achieving stable disease or remission before transplantation are critical for reducing post-transplant relapse. This requires preparatory regimens that maximize leukemia cell removal without increasing side effects. Clinical experience shows that the low selectivity of traditional chemotherapy drugs for leukemia cells is an important factor for pretransplant preconditioning. Therefore, improving selectivity with targeted drugs, such as inhibitors of BCR-ABL or FLT3, as well as targeting LSCs, may offer treatment breakthroughs[152,153].

Table 4 Main factors for post-hematopoietic stem cell transplantation relapse

Factors	Brief description	Ref.
Disease type	The relapse rate is highest in ALL patients, followed by AML patients and CML patients	[161]
Pretransplant disease status	The risk of relapse is significantly higher in nonremission patients and patients with a high level of residual leukemia cells before transplantation	[151]
Risk stratification	The level of risk is positively correlated with the relapse rate and negatively correlated with the disease-free survival rate	[162]
Stem cell source	Peripheral blood stem cells contain more lymphocytes with a more potent GVL effect; as a result, the relapse rate of BMT is higher than that of PBSCT	[163,164]
Preconditioning	Myeloablative preconditioning is more effective in reducing post-transplant relapse than reduced intensity conditioning and nonmyeloablative preconditioning; T cell depletion is associated with increased relapse rates in CML and AML	[164,165]
GVHD	Post-transplant GVHD, especially cGVHD, is associated with a significantly lower relapse rate and a higher survival rate	[166,167]

ALL: Acute lymphoblastic leukemia; AML: Acute myeloid leukemia; BMT: Bone marrow transplantation; cGVHD: Chronic GVHD; CML: Chronic myeloid leukemia; GVHD: Graft versus host disease; GVL: Graft versus leukemia; PBSCT: Peripheral blood stem cell transplantation; Ref.: Reference.

Over the last decade, the tumor-specific killing prodrug strategy based on the high level of ROS in tumor cells has provided a novel method for improving chemotherapy selectivity, enhancing efficacy, and reducing side effects[154,155]. Recently, several studies confirmed through *in vivo* and *in vitro* experiments that ROS-responsive anticancer prodrugs with ROS-sensitive linkers have precise killing effects on various types of leukemia cells and do not damage normal cells[156-160]. However, ROS-responsive anticancer prodrugs are ineffective in clearing MRD because the level of intracellular ROS in quiescent LSCs may be too low to activate the prodrug system, thus sparing these LSCs[161-167].

Another mechanism involved in post-allo-HSCT relapse is HLA loss, which has been reported in HSCT from both unrelated donors as well as sibling donors. Loss of HLA antigens reduces the efficacy of the GVL effect and favors the immune escape of AML cells. In haploidentical HSCT, as there is no incompatible target to stimulate alloreactivity, the GVL effect remains low[168,169]. Wu *et al*[169] analyzed nearly 800 cases of AML and ALL that were subjected, following an ATG T cell-replete conditioning regimen, to haploidentical HSCT and delineated that relapse occurred faster in AML patients who experienced loss of HLA antigens *vs* those who did not (223 d *vs* 321 d, $P = 0.03$). The factors linked with HLA loss in AML were aGVHD (odds ratio = 4.84) and body mass index < 18.5 kg/m^2 (odds ratio = 0.10). Similarly, Jan *et al*[170] evaluated HLA loss in the setting of haploidentical HSCT and concluded that minor HLA antigens might be involved in the process of immune recognition.

Prevention and pre-emptive treatment of post-allo-HSCT relapse remain major challenges for hematologists who manage individuals diagnosed with AML. The choice of therapy is dictated by measurable residual disease levels. If MRD is undetectable, subjects should undergo maintenance therapy, whereas detectable MRD requires pre-emptive management strategies, *e.g.*, DLIs[171]. A recently published meta-analysis highlighted that FLT3 inhibitors are a safe and tolerable therapy option for individuals who undergo allo-HSCT for *FLT3*-mutated AML. The use of these pharmacological agents as maintenance therapy post-allo-HSCT was associated with prolonged overall and relapse-free survival, with no significant differences between the treatment and control groups in terms of non-relapse mortality, GVHD, or adverse events[172]. Moreover, sorafenib maintenance therapy following allo-HSCT for *FLT3*-mutated AML was linked with increased overall survival and reduced cumulative incidence of relapse in AML patients who were subjected to allo-HSCT in the first complete remission[173].

Similarly, Fathi *et al*[174] explored, in the setting of a clinical trial, the benefits of 100 mg/d enasidenib maintenance post-allo-HSCT for *IDH2*-mutated AML. In their investigation, 2-year progression-free survival was 69%, overall survival was 74%, and the cumulative incidence of moderate/severe GVHD and of relapse were 42% and 16%, respectively, with only 1 patient experiencing AML relapse while on enasidenib maintenance. Another attractive option for post-allo-HSCT maintenance in the management of AML is represented by hypomethylating agents, namely azacitidine and decitabine. A meta-analysis of 14 studies delineated that the use of hypomethylating agents in this setting was correlated with reduced rates of cumulative incidence of relapse and GVHD, as well as higher rates of overall and relapse-free survival *vs* observation only[175]. Similarly, the combination of low-dose decitabine and venetoclax, *i.e.* a BCL-2 inhibitor, was associated with lower lates of relapse in high-risk AML patients who received this combination as maintenance therapy post-allo-HSCT[171,175].

Many strategies have been developed for post-allo-HSCT relapse, including withdrawal of immunosuppressants, immunotherapy, DLI, radiotherapy and chemotherapy, molecular targeted drugs, and second transplantation. At present, DLI is the most used and most effective in clinical practice. However, the efficacy of DLI varies greatly for different types of hematological malignancies.

Clinical data show that DLI enables most patients with relapsed chronic myeloid leukemia to achieve CR in the early stage of relapse, while the remission rate is lower than 30% for patients with relapsed acute leukemia[169]. The main side effects of DLI are GVHD and pancytopenia. Data have indicated that, after DLI, aGVHD and/or cGVHD will be diagnosed in approximately one-third of the subjects. Moreover, 5%-20% of these individuals will experience treatment-related mortality following DLI[176, 177]. To reduce DLI-related side effects, transplant specialists are modifying traditional DLI. Clinical experience shows that several modification measures, such as selective deletion of $CD8^+$ cells and escalating cell dosage regimens, have decreased GVHD-related morbidity without any impact on the DLI-mediated effect of GVL[178]. However, these methods cannot completely eliminate the risk of GVHD. Currently, researchers are developing conditional suicide protocols utilizing the HSV-tk or fas receptor-derived genes to achieve selective killing at will of the transduced cells if uncontrollable GVHD develops[178].

Apart from DLIs, other cell-based therapies, such as a second allo-HSCT, as well as chimeric antigen receptor (CAR)-T and CAR-NK cell-based treatments, have been developed. A second allo-HSCT can be attempted in younger patients, in whom relapse occurs at least 6 mo after the first allo-HSCT and who already have a matched related donor following the first allo-HSCT. However, there is a current need to conduct prospective studies to assess the benefits and risk of a second allo-HSCT, as most data have been derived from retrospective investigations. Impressive overviews of a second allo-HSCT in the setting of relapsed AML post-allo-HSCT has been published elsewhere[171,179].

Hypomethylating agents, *i.e.* azacitidine and decitabine, IDH1/2 inhibitors, and venetoclax have been recognized as members of the therapeutic armamentarium in the setting of post-allo-HSCT AML relapse as well. In addition, immune checkpoint inhibitors (*e.g.*, ipililumab and magrolimab), monoclonal antibodies (gemtuzumab ozogamicin and the anti-IL3 agent CLS360) and vaccines are displaying promising results. In addition, several novel targeted agents are currently being developed and/or investigated[171,179]: Small-molecule inhibitors (apart from FLT3 inhibitors and the BCL-2 inhibitor venetoclax), trametinib (anti-MEK agent), glasdegib (a molecule that interacts with the Hedgehog pathway), and uproleselan (anti-E-selectin agent); histone-deacetylase inhibitors, panobinostat; and IDH1/2 inhibitors, ivosidenib and enasidenib.

In addition, the survival of individuals who have undergone allo-HSCT is also affected by the compatibility of specific HLA loci of the donor and recipient. A recent publication pointed out that HLA matching and the age of the recipient are simple factors that can accurately stratify subjects into prognostic groups as well as predict overall survival and non-relapse mortality in allo-HSCT[180]. However, a meta-analysis of 19 investigations with a patient sample of 3336 individuals concluded that mismatched allo-HSCT from unrelated donors remains a safe procedure that is linked with favorable outcomes[181].

Furthermore, several predictors of relapse in haploidentical HSCT have been identified. For example, as compared to intermediate cytogenetic risk, higher relapse rates and shorter overall survival were noted in patients diagnosed with AML with adverse risk cytogenetic abnormalities who were subjected to haploidentical HSCT without T cell depletion[182]. Pre-allo-HSCT MRD levels are also implicated in the outcome of haploidentical HSCT. Zhang *et al*[183] demonstrated that AML subjects with undetectable MRD pre-allo-HSCT registered elevated overall survival and disease-free survival *vs* MRD-positive cases. In addition, cumulative incidence of relapse was similar between MRD-positive and MRD-negative cases in the setting of haploidentical allo-HSCT, which was also linked with a better prognosis *vs* HLA-matched allo-HSCT for individuals who remained MRD-positive pre-allo-HSCT.

Similarly, Al Hamed *et al*[184] identified predictors of relapse in *NMP1*-mutated AML individuals who were subjected to haploidentical HSCT. Detectable MRD pre-allo-HSCT, presence of *FLT3* mutations, and allo-HSCT in the second complete remission negatively impacted leukemia-free survival and were linked with elevated percentages of relapsed cases. Overall survival was shorter in cases with concomitant detectable MRD pre-allo-HSCT, presence of *FLT3* mutations, and older age, whereas haploidentical HSCT was correlated with elevated overall survival rates. Similarly, Canaani *et al*[185] confirmed that MRD status pre-allo-HSCT was a predictor of relapse following haploidentical HSCT. Undetectable MRD was correlated with elevated percentages of leukemia-free survival and reduced relapse rates, whereas haploidentical HSCT in MRD-positive AML cases was linked with better outcomes when the donor had anti-cytomegalovirus antibodies.

In recent years, with continuous advancements in immunology, novel cellular immunotherapies such as CAR-T cells have emerged and are being investigated in clinical trials, generating certain effects, such as significantly enhancing the capacity of immune cells to specifically recognize and kill leukemia cells. However, there are some obstacles for the clinical application of CAR-T cell therapy. For example, CAR-T cells target only cover certain types of leukemia, with a risk of attacking normal tissues and cells due to off-target effects and an inflammatory storm. Moreover, more research is needed to validate the long-term effects of CAR-T cell therapy[186-189]. The implementation of CAR-T cell therapy in AML is extremely challenging as the targeted antigen needs to be primarily expressed by AML blast cells and not by hematopoietic cells, activated T cells, or other cells in the body. In addition, the targeted antigen should be involved in or be a driver of the proliferation of AML blast cells as well as be present solely on AML blast cells and LSCs.

Currently, the following antigens have been studied as potential targets of CAR-T cell therapy in AML: CD33, CD123, CD38, FLT3, Lewis Y, NKG2D ligand, CD116, CD117, CD70, CD93, CD44v6, CD276, CLL1, ILT3, TIM-3, Siglec-6, FRβ, h8F4, and the PR1/HLA-2 complex. Moreover, antigen pairs have also been studied by molecular biology techniques, with several research teams identifying CD33+ADGRE2, CLEC12A+CCR1, CD33+CD70, CD33+TIM3, CLL1+TIM3, CLL1+CD123 and CLL1+CD33 as potential candidates for the "ideal antigen" for CAR-T cell therapy. Furthermore, as the manufacture of autologous CAR-T cells can require several weeks, the development of allogeneic CAR-T and allogeneic CAR-NK cell therapies has also been taken into consideration but has failed to produce satisfactory results in the management of AML due to toxicity.

Another potential future strategy is to target AML-associated, *e.g.*, WT1 or PR1, rather than AML-specific antigens using peptide vaccines[137,190,191]. However, at present, allo-HSCT remains the standard of care for individuals diagnosed with AML and who display evidence of intermediate or unfavorable risk, and the potential benefits of CAR-T cell therapy in conjunction with pharmacological agents and/or allo-HSCT in the management of AML remains to be decided in future studies[192].

In addition, other cell-based therapies, such as CAR-NK cell therapies, have emerged from the drug pipeline landscape. Ureña-Bailén *et al*[193] reported that NK-92 cells transduced with CD276-CAR constructs with a triple knock-out of CBLB, NKG2A, and TIGIT (inhibitory checkpoints of NK cells), CD276-CAR-NK-92 with CBLB knock-out as well as CD276-CAR-NK-92 with TIGIT knock-out exerted significant cytotoxicity against cellular models of AML. Similarly, CD123-CAR-NK constructs exhibited antileukemic potential and a satisfactory safety profile in a cellular model of CD123+ AML[194]. Similarly, *NPM1*-mutation-specific T cell receptor-like CAR cytokine-induced memory-like NK cell constructs displayed significant antileukemic potential against a cellular model and patient-derived *NMP1*-mutated AML samples[195]. Thus, we hypothesize that NK-CAR constructs might emerge as future therapies of AML.

Monitoring is critical for the prevention and treatment of post-allo-HSCT relapse. It also plays an important role in the long-term survival of leukemia patients. Flow cytometry is useful for identifying leukemia-related abnormal phenotypes, real-time quantitative PCR can be used to detect leukemia-specific fusion genes, and fluorescence *in situ* hybridization can detect specific chromosomal translocations or deletions. These methods can be used to monitor MRD to facilitate the early detection of post-transplant relapse[196,197].

In recent years, next-generation sequencing technology has been widely used in the clinic. Because next-generation sequencing has the advantages of high throughput, accurate quantification and high sensitivity, it is of great significance for evaluating the curative effect, guiding treatment and predicting relapse[198]. In addition, graft mosaicism is a highly sensitive measure for predicting relapse and guiding immune intervention[199]. MRD monitoring may be combined with graft mosaicism monitoring. In cases of elevated MRD or decreased donor mosaicism, immunosuppressants may be reduced or stopped, and targeted drugs or DLI may be used for timely intervention[200-202]. Currently, no consensus has been established for the frequency of and cutoff values for MRD and graft mosaicism monitoring, and the technologies and methods must be further standardized. Moreover, further research is needed to investigate the timing of monitoring, how fast to reduce or stop immunosuppressants, the timing of DLI, and the number of cells infused.

OTHER COMPLICATIONS OF ALLO-HSCT

Although only briefly discussed in this narrative review, allo-HSCT can also be associated with various complications. A serious complication of allo-HSCT is graft failure. Graft failure can be either primary, *i.e.* HSCs from the donor fail to engraft at all, or secondary, *i.e.* HSCs from the donor engraft successfully but a loss of donor cells occurs at some time point[203,204]. In addition, poor graft function has also been identified as a complication of allo-HSCT, yet it must be differentiated from graft failure. In both graft failure and poor graft function, cytopenias are present, the bone marrow is hypocellular, and there is no evidence of relapse. In terms of chimerism, poor graft function is associated with full-donor chimerism, whereas in graft failure it is either full-recipient or mixed. Initial donor engraftment is noted in both primary and secondary poor graft function, and also in secondary graft failure but not in primary graft failure. However, initial hematological recovery only occurs in secondary graft failure and secondary poor graft function, whereas it is absent in both primary graft failure and primary poor graft function.

Risk factors for graft failure include major ABO incompatibility, HLA mismatch, pretransplantation MRD and disease type, stem cell source and dose, conditioning regimen, and others, whereas poor graft function seems to be influenced more by the presence of BM fibrosis, damage to HSCs or stromal cells caused by the selected conditioning regimen or other pharmacological agents, infections, or GVHD as well as a low infusion dose of HSCs. Graft failure, poor graft function, and their management have been reviewed elsewhere[203,204].

In addition, apart from cGVHD, allo-HSCT poses the threat and several late onset complications that can develop in the context of GVHD or accompany it. Late-onset complications of allo-HSCT can affect

the skin and mucosa, eyes, gastrointestinal tract, lungs (*e.g.*, bronchiolitis obliterans syndrome), muscles and connective tissue, endocrine system and the metabolism (hypogonadism, thyroid dysfunction, osteoporosis, diabetes), kidneys, nervous system, and/or the heart. In addition, infections (*e.g.*, with viruses such as varicella zoster virus, Epstein-Barr virus, or cytomegalovirus reactivation, fungi, or encapsulated bacteria) and the development of secondary malignancies in allo-HSCT recipients have emerged as "swords of Damocles" in the survival of AML patients in the post-allo-HSCT setting. These complications have been discussed in detail elsewhere[205,206].

A recent investigation of over 40000 leukemia patients who were subjected to allo-HSCT revealed that the most frequent late-onset complications of this therapeutic procedure were azoospermia (approximately 71.0%), cGVHD (5-year post-allo-HSCT prevalence at approximately 43.0%), secondary malignancies (20-year post-allo-HSCT prevalence at approximately 21.0%), depression (post-allo-HSCT prevalence at approximately 18.0%), hypothyroidism (15-year post-allo-HSCT prevalence at approximately 11.0%), bronchiolitis obliterans syndrome (4-mo post-allo-HSCT prevalence at approximately 10.0%), cardiovascular disease (15-year post-allo-HSCT prevalence at approximately 7.5%), and avascular necrosis (10-year post-allo-HSCT prevalence at approximately 5.0%)[207]. However, future prospective studies are needed to clarify the exact epidemiology of late complications of allo-HSCT.

Future directions of research in the field of allo-HSCT should also focus on potential opportunities in this expanding field, such as the combination of allo-HSCT with CAR-T cell based therapies, the application of novel drugs in conditioning regimens, the use of ATG in combination with post-transplant cyclophosphamide, and others.

CONCLUSION

With continuous developments in immunology, molecular biology, and related disciplines, allo-HSCT is advancing rapidly with proven results and has emerged as a key factor in the management of AML. In recent years, with improved preconditioning regimens, optimized donor selection strategies, novel targeted drugs, and monoclonal antibodies, the incidence and severity of transplant-related complications have been greatly reduced, and the long-term survival of leukemia patients after allo-HSCT has significantly improved. In-depth research on the molecular mechanisms that drive AML will ensure the development of better treatments to further improve remission, prevent relapse, manage early and late onset complications of allo-HSCT, and improve patient survival.

FOOTNOTES

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REVIEW

Idiopathic hirsutism: Is it really idiopathic or is it misnomer?

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Abstract

Hirsutism, which is characterized by excessive growth of terminal hair in a male pattern, may result from various causes including polycystic ovary syndrome (PCOS), non-classic congenital adrenal hyperplasia, adrenal or ovarian tumors or it may be idiopathic. Idiopathic hirsutism is currently defined as hirsutism associated with normal ovulatory function, normal serum androgen levels and normal ovarian morphology, however, the pathogenesis of idiopathic hirsutism is not clear. The androgens are the main hormones to stimulate growth of body hair, therefore, there should be any form of increased androgen effect irrespective of normal serum androgen levels in any patient with hirsutism. In accordance to this scientific truth, we have previously shown that, although within normal limits, patients with idiopathic hirsutism have relatively higher serum androgen levels (relative hyperandrogenemia) in comparison to healthy subjects which let as to think that is idiopathic hirsutism really idiopathic? In addition to relative hyperandrogenemia, we have previously shown that, in comparison to healthy subjects, women with idiopathic hirsutism demonstrated higher expression of steroid sulphatase and 17-beta hydroxysteroid dehydrogenase mRNA both in the subumbilical region and arm skin, which contributes to local androgen metabolism. Those results support the idea that, in some patients, although the adrenals or ovaries do not secrete increased amount of androgens leading to hyperandrogenemia, pilocebaceous unit locally produce increased amount of androgens leading to hirsutism without ovulatory dysfunction. Upon the demonstration of relative hyperandrogenemia and possible increase in local androgen synthesis in patients with idiopathic hirsutism, we think that idiopathic hirsutism is not idiopathic and it may be named as "normoandrogenic hirsutism". Furthermore, it may not be a different entity but may be an early stage of hyperandrogenic disorders such as PCOS. Clinically, this can be find out by

following-up patients with idiopathic hirsutism prospectively.

Key Words: Idiopathic hirsutism; Normoandrogenic hirsutism; Hyperandrogenemia; Androgen excess disorders

Core Tip: Idiopathic hirsutism (IH) is defined as hirsutism associated with normal ovulatory function, normal ovarian morphology and normal serum androgen levels, however, its pathogenesis is not clear. We have previously shown that, patients with IH have relatively higher serum androgen levels and demonstrated higher expression of steroid sulphatase and 17-beta hydroxysteroid dehydrogenase mRNA both in the subumbilical region and arm skin, which contributes to local androgen metabolism. Upon the demonstration of relative hyperandrogenemia and possible increase in local androgen synthesis in patients with IH, we think that idiopathic hirsutism is not idiopathic and it may be named as "normoandrogenic hirsutism".

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INTRODUCTION

Hirsutism is a common clinical condition which affects approximately 5%-15% of premenopausal women. It is typically defined as excessive growth of terminal hair in a male pattern. Hirsutism has a significant negative impact on quality of life and makes a severe psychological distress in women. The occurrence of hirsutism is affected from local androgen concentrations, the interaction between various androgens in serum, and ultimately, sensitivity of the hair follicle to androgens. Hirsutism may be seen as a result of polycystic ovary syndrome (PCOS), non-classic congenital adrenal hyperplasia, ovarian or adrenal tumors or it may be idiopathic[1-4]. The most common causes of hirsutism among premenopausal women are PCOS and idiopathic hirsutism. While measurable hyperandrogenemia has been detected in 80%-90% of women with hirsutism, the severity of hirsutism and the level of androgen excess are not well-correlated. A well-known example of this condition is idiopathic hirsutism which is characterized by normal serum androgen levels[5-7]. Apart from idiopathic hirsutism, all the other causes of hirsutism are associated with hyperandrogenemia, thus, the diagnosis of idiopathic hirsutism requires exclusion of other disorders. Although some mechanisms have been proposed, the pathogenesis of idiopathic hirsutism is not well known and in this review we will discuss the potential mechanisms underlying idiopathic hirsutism.

WHAT IS KNOWN ABOUT IDIOPATHIC HIRSUTISM?

Over the last years the diagnostic criteria of idiopathic hirsutism have changed. In early reports, idiopathic hirsutism has been defined as "hirsutism of unknown cause" irrespective of serum androgen levels[8-10]. However, investigations related to various androgen excess disorders changed the definition of idiopathic hirsutism. Currently, idiopathic hirsutism is diagnosed in hirsute women who have regular ovulatory cycles, normal ovarian morphology and normal serum androgen levels. Since the pathogenesis of idiopathic hirsutism is not well known, in contrast to other androgen excess disorders, no clear molecular or biochemical markers exist in patients with idiopathic hirsutism[11]. The prevalence of idiopathic hirsutism has been reported between 6%-16% in various populations[3,12,13]. A brief summary regarding the pathogenesis of idiopathic hirsutism is given in Table 1.

Functional hyperandrogenism

Although huge number of studies have been performed for the pathogenesis of PCOS, only limited number of investigations exist regarding the pathogenesis of idiopathic hirsutism. Escobar-Morreale *et al*[14] investigated the ovarian and adrenal steroidogenic abnormalities in 24 patients with idiopathic hirsutism by using ACTH stimulation test and GnRH analog test. They found that women with idiopathic hirsutism show an increased ovarian 17-hydroxyprogesterone secretion and a minimally increased adrenal 17-20 Lyase activity, suggesting that these patients have mild forms of ovarian and

Table 1 Overview of pathogenetic mechanisms in idiopathic hirsutism

Suggested/Established mechanisms	How to contribute to hirsutism
Functional hyperandrogenism	Milder forms of ovarian and adrenal androgen hypersecretion
5α-reductase activity	Leading to increased DHT level which is a potent androgen
Androgen receptors	Some forms of AR variances leads to increased receptor activity
Aromatase enzyme (dys)function	Decreased aromatase activity leads to relative hyperandrogenemia at tissue level and possibly in the circulation
Local androgen production	Pilocebaceous unit locally produce increased amount of androgens
Insulin resistance	Althouhg its role in IH is not clearly established as seen in PCOS, concomitant hyperinsulinemia may contribute to hyperandrogenism

DHT: Dihydrotestosterone; AR: Androgen receptor; IH: İdiopathic hirsutism; PCOS: Polycystic ovary syndrome.

adrenal functional hyperandrogenism[14]. Rossi *et al*[15] evaluated the ovarian and adrenal gland functions in 48 women with idiopathic hirsutism by using ACTH stimulation and GnRH analog test. The authors found mild functional ovarian and adrenal hyperandrogenism and suggested as an underlying mechanism of idiopathic hirsutism.

5α- reductase activity

The androgens found in women include testosterone, androstenedione and dehydroepiandrosterone sulfate (DHEAS). Testosterone is converted to dihydrotestosterone (DHT) *via* the enzyme 5α-reductase and DHT has much more affinity to androgen receptor (AR) intracellularly. The most active androgen, DHT, has low serum levels since it is synthesized in androgen target tissues.

Although most literature was old, several studies showed an increased level of 5α-androstane-3α, 17 beta-diol (3α-diol) and 3α-diol glucuronide (3α-diol-G) which were metabolites of DHT in patients with idiopathic hirsutism[16-18]. Serum 3α-diol-G level has been shown a good correlation with the severity of hirsutism in idiopathic hirsute cases, however, those metabolites do not seem to exert androgenic effects, rather they reflect testosterone and DHT production and are considered as a marker of 5α-reductase activity[19].

5α-reductase activity was also evaluated in skin samples of patients with idiopathic hirsutism and PCOS and the authors demonstrated an increased conversion of testosterone to DHT and DHT to 3α-diol. Those results suggest an increased 5α-reductase activity in hyper and normoandrogenic phenotypes of hirsutism[20]. Currently, increased skin 5α-reductase activity is considered as the main pathophysiologic abnormality of idiopathic hirsutism, leading to increased tissue synthesis of DHT and possibly an alteration in androgen receptor function[21-23].

Abnormalities in androgen receptor and its function

Androgens exhibit their effect *via* the AR and dysfunctional AR may contribute to variable phenotypes of androgenicity. The AR gene is located on the X-chromosome and this gene contains a polymorphic trinucleotide repeat (CAG). Variances in the AR sequence are mostly identified by tandem repeat polymorphisms (number of CAG repeats) and methylation pattern of AR gene. It has been shown that the transcriptional activity of the AR is inversely correlated with the number of CAG repeats[24]. The allels with shorter CAG repeat length are associated with amplified AR activity. We have recently shown that, as in PCOS patients, AR exon 1 CAG repeat length distrubition was different in patients with idiopathic hirsutism than control subjects leading to the development of hirsutism *via* increased androgen effect[25]. On the other hand, Vottero *et al*[26] did not find any difference in the number of CAG repeats between patients with idiopathic hirsutism and control subjects. Thus, the role of AR abnormalities in the pathogenesis of idiopathic hirsutism require further studies.

Aromatase enzyme (dys)function

Previously, we have shown that, although the patients with idiopathic hirsutism have normal serum androgen levels, these patients have relatively higher serum androgen levels and lower estradiol levels in comparison to healthy subjects[27]. In other words, those patients were actually hyperandrogenic, however, by using some cut-off values derived from the reference values of commercial kits, we diagnose these patients as idiopathic hirsutism. Moreover, these patients show decreased estradiol/testosterone ratio, which is a product of aromatase activity, leading to relative hyperandrogenemia[27]. Thus, instead of measuring serum androgen levels alone, when estradiol/testosterone ratio was compared with healthy subjects, patients with idiopathic hirsutism have reduced levels than healthy subjects indicating that these patients are also hyperandrogenic. Mahmoudieh *et al*[28] investigated the cardio-metabolic risks in 334 women with idiopathic hirsutism and compared the results with 1226

control subjects over a 16-year study period. Similar to our results, they also showed that idiopatic hirsute women had relatively higher serum androgen levels compared to healthy subjects. So, the main question is why we still call those patients as idiopathic?

The current diagnosis of idiopathic hirsutism relies on normal serum androgen levels which are almost determined by immunoassays. However, the standards and limitations of those assays are matter of debate during the last years[29]. The Endocrine Society has suggested using liquid chromatography/tandem mass spectrometry (LC-MS/MS) for measuring steroid hormones, particularly testosterone[30]. In the only study from existing literature evaluating hyperandrogenemia by LC-MS/MS in patients with idiopathic hirsutism, the authors found that cut-off values for testosterone was lowered[31]. This implies that patients with idiopathic hirsutism may have underestimated serum androgen levels which were not determined by immunoassays.

Local androgen production

Recently, we thought that increased local androgen production may also be the underlying cause of idiopathic hirsutism since skin tissue have all the enzymes required for androgen biosynthesis and catabolism indicating that it behaves as an independent peripheral endocrine organ[32,33]. Similarly, as seen in acne and androgenetic alopecia, an association between possible local overproduction of active androgens and skin disorders has been suggested[34].

Previously, it has been shown that steroidogenic acute regulatory protein, cytochrome P450 cholesterol side-chain cleavage (P450scc) and cytochrome P450 17α hydroxylase (P450c17) have been expressed in the cutaneous tissue suggesting that cholesterol derived in skin tissue could be further used as a substrate for *de novo* steroid hormone synthesis in human epidermis and the sebaceous gland [34]. In fat cells and hair follicles aromatase play a "detoxifying" role by metabolizing excess androgens locally and disturbances in this metabolism may contribute to hirsutism[34]. Moreover, in the skin, testosterone, which is the potent tissue androgen, results from the conversion of circulating DHEAS, through the serial enzymatic activities of steroid sulfatase, 3β-hydroxysteroid dehydrogenase and 17β-HSD[35]. In vitro experiments showed that different skin cells have different duties concerning the presence and activity of androgen metabolism. While keratinocytes degrade androgens, sebocytes are capable of synthesing testosterone from adrenal precursors and to inactivate it, thus contributing to maintain androgen homeostasis[32,35,36]. The enzyme 17β-HSD type 2 inactivates both testosterone and estradiol to androstenedione and estrone, respectively[37]. Overall, the skin and its appendages have been equipped with the necessary enzymes for androgen synthesis and metabolism. Physiologic levels of these enzymes found in normal conditions may be upregulated and contribute to peripheral hyperandrogenism in several pathologic conditions.

In patients with idiopathic hirsutism, we have freshly obtained hair follicles and investigated the mRNA expression of enzymes having a role in locally produced androgens and their precursors[38]. We have shown that, women with idiopathic hirsutism exhibited higher expression of *HSD17B2* and steroid sulphatase (STS) mRNA both in the subumbilical region and arm skin when compared to healthy women, suggesting the contribution of these enzymes to local androgen metabolism. In women with idiopathic hirsutism, increased mRNA expression may be considered as a clue for the tendency to local hyperandrogenemia although we did not measure the STS enzyme activity. Moreover, increased mRNA expression of STS was also found in the arm skin without hair. This suggests an overall increased expression of this enzyme in idiopathic hirsute patients. In the skin biopsies, we have also shown that mRNA expression of *IL6* is significantly lower in patients with idiopathic hirsutism than healthy subjects. This was an important finding since *IL6* affects aromatase expression. Estrogen biosynthesis in human body is higly complex organization and various hormones may activate or inactivate the regulation of aromatase expression in human cells[39]. We can speculate that local synthesis of estrogen may be negatively affected by (indirect) effect of aromatase activity. Unfortunately, there is not adequate data regarding the molecular mechanisms in the pathogenesis of idiopathic hirsutism.

All those results support the idea that, in some patients, although the adrenals or ovaries do not secrete increased amount of androgens leading to hyperandrogenemia, pilocebaceous unit locally produce increased amount of androgens leading to hirsutism without ovulatory dysfunction. Thus, patients with idiopathic hirsutism may have an increased androgen synthesis within the skin tissue so, calling those patients as "idiopathic" is misnomer. In that scenario, patients with idiopathic hirsutism may be a very early stages of PCOS and this can be answered only long term follow-up of those patients whether they will represent hyperandrogenemia in the future or not. If so, another question is what may be the factor determining transition of idiopathic hirsutism to PCOS phenotype?

Insulin resistance and idiopathic hirsutism

Insulin resistance and associated hyperinsulinemia seem one of the most important factor in androgen excess disorders[40]. Unlühizarci *et al*[27] and some others[41,42] showed that patients with idiopathic hirsutism may also have insulin resistance and it is more prominent in overweight or obese patients. Amiri *et al*[43] made a meta-analysis to investigate the relationship between insulin resistance and idiopathic hirsutism. In addition to demonstrating altered metabolic parameters and insulin resistance in patients with idiopathic hirsutism, the authors suggest that increased peripheral androgen activity in women with idiopathic hirsutism is associated with insulin metabolism. We have previously shown that

18.7% of the patients with idiopathic hirsutism had impaired glucose tolerance (IGT) and more importantly, we found that after excluding the patients with IGT, the patients were still demonstrating insulin resistance[27]. It is well known that in the presence of insulin resistance and hyperinsulinemia patients with hirsutism exhibit more advanced metabolic and reproductive symptoms. Moreover, weight loss and decreased insulin resistance resumes menses and improves hyperandrogenemia in patients with PCOS. Thus, if our hypothesis is correct, insulin resistance may be the triggering factor in the transition of patients with idiopathic hirsutism to PCOS phenotype.

Androgens produced by alternative pathways

On the other hand, 11-oxygenated C19 steroids are important androgens and have been shown to have a role in patients with PCOS or congenital adrenal hyperplasia[44]. These steroids have been shown to stimulate androgen receptors similar or greater than testosterone or DHT. It may be possible that these 11-oxygenated C19 steroids may have a role in patients with idiopathic hirsutism, however, their serum levels are not routinely measured by commercial assays[31,44]. We think that this is an interesting candidate area of scientific research for exploring the pathogenesis of idiopathic hirsutism.

IDIOPATHIC HIRSUTISM: IS IT A MISNOMER?

Currently, idiopathic hirsutism is defined as hirsutism associated with normal serum androgen levels, normal ovarian morphology and ovulatory functions[5]. It is well known that dermal papilla plays a fundamental role in the regulation of hair growth, and cells of dermal papilla seem to have the primary role of androgen regulation of hair growth[6,7]. There should be any form of increased androgen level or effect even in patients with idiopathic hirsutism since androgens are the main hormones to stimulate growth of body hair. Even though those patients have normal serum androgen levels, they suffer from a hyperandrogenic sign, namely hirsutism and we think that idiopathic hirsutism is not idiopathic and it may be named as "normoandrogenic hirsutism", furthermore, it may not be a different entity but may be an early stage of hyperandrogenic disorders such as PCOS.

In various endocrine disorders, even serum levels of hormones are within normal limits, locally produced hormones may be higher and clinically important. By analogy, patients with subclinical hyperthyroidism have normal serum thyroid hormone levels (in addition to suppressed serum TSH level) but an increased tissue response exist leading to thyrotoxic manifestations such as tachycardia. We speculate that the same situation exist in patients with idiopathic hirsutism and by the time, those patients may show increased serum androgen levels similar to overt hyperthyroid patients. We suggest that normal serum androgen levels do not always mean to expose normal androgen effect on skin.

CONCLUSION

By definition, although idiopathic hirsutism is characterized by normal serum androgen levels, those patients exhibit hirsutism and in the presence of scientific data/evidences on relative hyperandrogenemia, increased local androgen production, insulin resistance (although not universal), AR polymorphism and increased DHT production we think that idiopathic hirsutism is misnomer and it is not actually idiopathic. As discussed above, it has more complex pathogenesis than any other androgen excess disorder such as congenital adrenal hyperplasia which is characterized by steroidogenic enzyme deficiencies. Thus, instead of idiopathic, we suggest "normoandrogenic hirsutism" until a more appropriate name is found. Furthermore, it may not be a different entitiy but may be an early stage of hyperandrogenic disorders such as PCOS. Clinically, this can be find out by following-up patients with idiopathic hirsutism prospectively. Additionally, by establishing the pathogenesis/underlying mechanisms of idiopathic hirsutism, new therapeutic strategies may be offered.

FOOTNOTES

Author contributions: Unluhizarci K performed the majority of the writing; Hacioglu A contributed to drafting the manuscript; Karaca Z contributed to the writing and made critical suggestions; Taheri S performed the experimental studies in our instution; Kelestimur F approved the final version of the manuscript to be published; all authors have read and approve the final manuscript.

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MINIREVIEWS

Liver function in transgender persons: Challenges in the COVID-19 era

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Abstract

Transgender persons constitute a non-negligible percentage of the general population. Physical gender-transitioning in trans persons is mainly achieved with hormonal cross-sex therapy and sex reassignment surgeries that aim to align bodily appearance with gender identity. Hormonal treatment acts *via* suppressing the secretion of the endogenous sex hormones and replacing them with the hormones of the desired sex. The administration of testosterone is the typical masculinizing treatment in trans men, whilst trans women are routinely treated with estradiol agents in combination with anti-androgens or gonadotrophin-releasing hormone agonists if testes are present. Exogenous androgenic steroids, estradiol agents, and anti-androgens have been implicated in a series of hepatotoxic effects. Thus, liver integrity is a major concern with the long-term administration of cross-sex therapy. Hepatic tissue is susceptible to coronavirus disease 19 (COVID-19) through various pathophysiological mechanisms. Special consideration should be paid to minimize the risk of hepatic damage from the potential cumulative effect of COVID-19 and gender-affirming treatment in transgender patients. Appropriate care is significant, with continuous laboratory monitoring, clinical observation and, if needed, specific treatment, especially in severe cases of infection and in persons with additional liver pathologies. The pandemic can be an opportunity to provide equal access to care for all and increase the resilience of the transgender population.

Key Words: Transgender persons; Drug induced liver injury; COVID-19

Core Tip: Transgender persons may account for approximately up to 0.3% of the population. Their access to health care and medications may be hampered in the coronavirus disease 19 (COVID-19) era. The effects of COVID-19 *per* se on the liver may not be negligible. In this concise review we ponder on these effects, honed on transgender persons.

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INTRODUCTION

In humans, as in most mammals, biological sex is determined by sex chromosomes X and Y. The development to a male or female sex depends on the presence of a single sex-regulatory genetic locus, the sex-determining region Y (SRY) gene, on the male-limited Y chromosome. Expression of SRY early in the embryonic life leads the bipotential embryonic gonad to differentiate into testis through the activation of male-specific developmental pathways. In contrast, ovaries develop when SRY is absent. The first signs of sexual differentiation of gonads occur by the sixth gestational week in humans. Sex hormones induce further sexual differentiation in gonads and non-gonadal tissues and organs and in this way, they form the sex phenotype[1].

Gender identity is a person's self-perception of belonging to a particular gender type (masculine, feminine, a combination, or none of both) and does not always align with biological sex. Gender dysphoria is the sense of distress which derives from the discordance between an individual's gender identity and sex features[2]. The term 'transgender' refers to persons whose gender identity (and possibly gender expression) differs from what is normative for their biological sex (most usually assigned at birth). In particular, transgender males (trans men) are persons who self-identify as male, although they were labeled as female at birth and transgender females (trans women) are persons who have the gender identity of a female, despite having been assigned male sex at birth. Furthermore, the transgender term also includes persons whose gender identity does not conform to the classical dipole of male/female[3]. It is estimated that about 0.355% of the population identify themselves as transgender. However, the prevalence of trans people who receive medical care for gender-transitioning is only around 0.009%[4].

After the diagnosis of gender dysphoria is established and if physical transitioning is desired, a framework for ongoing care needs to be applied. An appropriate management may include psychotherapy, hormonal treatment, and surgical sex reassignment. These approaches are considered to be safe and effective both in short- and in the long-term[5]. Gender-affirming hormonal treatment improves uneasiness from perceived inconsistencies between one's biological sex and gender identity. It acts *via* suppressing the secretion of the endogenous sex hormones and replacing them with the hormones of the desired sex. As with any medical therapy, the awareness of potential side effects is important. Thus, regular clinical evaluation for physical changes and laboratory monitoring of potential adverse effects in response to cross-sex hormonal therapy is necessary. Typical follow-up is performed every three months during the first year of treatment and then once or twice yearly[6]. Tables 1 and 2 depict a model timeline for monitoring clinical course and laboratory parameters when treating trans men and women, respectively.

HEALTH CARE FOR TRANSGENDER PEOPLE

Transgender people have a series of special medical needs which create an inevitable regular engagement with health care services. In terms of psychiatric care, a firm diagnosis of gender dysphoria and subsequently psychotherapy on finding ways to integrate each person's diverse gender identity into the personal background and social circumstances are fundamental. Trans people often encounter stigmatization and discrimination which can have a profound adverse effect on their emotional well-being. Therefore, they need to access responsive and competent mental health services to cope with depression, suicidality, anxiety, and substance use which are disproportionally frequent among transgender populations[7,8].

Gender-transitioning is performed with medical interventions, including hormonal therapy and sex reassignment surgeries that aim to align physical appearance with gender identity. Typical trans-feminine (male-to-female) hormonal treatment includes estrogens and testosterone-lowering agents, such as anti-androgens or gonadotrophin-releasing hormone (GnRH) agonists, whilst the administration of testosterone is the mainstream approach in transmasculine (female-to-male) hormonal

Table 1 Timeline for monitoring trans men

Laboratory evaluation	
Baseline blood tests	Testosterone, estradiol; CBC (including Hct or Hgb); Liver enzymes, lipid profile, creatinine; Fasting glucose (and HbA1c or oral glucose tolerance test if diabetes is suspected)
4-6 wk after starting treatment	Testosterone, estradiol; CBC (including Hct or Hgb)
3, 6, 9, and 12 mo after starting treatment	Testosterone, estradiol; CBC (including Hct or Hgb); Liver enzymes, lipid profile, creatinine (every 6 mo); Fasting glucose (every 6 mo)
Semiannually or annually thereafter	Testosterone, estradiol; CBC (including Hct or Hgb); Liver enzymes, lipid profile, creatinineFasting glucose (every 6 mo)
In 50 yr of age (only if treatment is stopped or when risk factors for osteoporosis exist) and accordingly thereafter	Bone mineral density measurement
Individualized approach	Screening tests for breast and endometrial cancer (with no prior hysterectomy)
Clinical assessment	
Regular clinical examination (including body weight and blood pressure measurements), evaluation of masculinization, recording and monitoring of potential side effects	

CBC: Complete blood count; Hct: Hematocrit; Hgb: Hemoglobin; HbA1c: Glycated hemoglobin.

Table 2 Timeline for monitoring trans women

Laboratory evaluation	
Baseline blood tests	Testosterone, estradiol; Prolactin; CBC; Liver enzymes, lipid profile, creatinine; Fasting glucose (and HbA1c or oral glucose tolerance test if diabetes is suspected); Electrolytes; Coagulation tests (in case of high risk for thrombosis)
1 mo after starting treatment	CBC; Liver enzymes, lipid profile, creatinine; Electrolytes (if taking spironolactone)
3, 6, 9, and 12 mo after starting treatment	Testosterone, estradiol; CBC; Liver enzymes, lipid profile, creatinine (every 6 mo); Fasting glucose (every 6 mo); Electrolytes (if taking spironolactone)
Semiannually or annually thereafter	Testosterone, estradiol; Prolactin (every 2 yr); CBC; Liver enzymes, lipid profile, creatinine; Fasting glucose (every 6 mo); Electrolytes (if taking spironolactone)
In 60 yr of age (or earlier if treatment is stopped after orchiectomy or when risk factors for osteoporosis exist) and accordingly thereafter	Bone mineral density measurement
Individualized approach	Screening tests for prostate and breast cancer
Clinical assessment	
Regular clinical examination (including body weight and blood pressure measurements), evaluation of feminization, recording and monitoring of potential side effects	

CBC: Complete blood count; Hct: Hematocrit; Hgb: Hemoglobin; HbA1c: Glycated hemoglobin.

therapy. The goal is to achieve and maintain sex hormone levels in the normal physiologic range of the desired gender. For non-binary persons, regimens and dosages should be modified according to the clinical targets[9]. Surgical reconstruction techniques focus on transforming genitals and secondary sex characteristics[10]. Hence, the process of gender-transitioning is inextricably related to the utilization of specialized medical services.

Trans people have special sexual and reproductive medical needs. Comprehensive cancer screening based on the retained organs[11] and prevention and management of sexually transmitted diseases[12] are important aspects of transgender care. Further possible needs for health services are linked to gamete storage and assisted reproduction[13]. Nonetheless, caring for transgender individuals also includes general coverage for possible co-existing morbidities which are not directly related to gender-transitioning.

IMPACT OF THE COVID-19 PANDEMIC ON TRANSGENDER HEALTH CARE

As a medically and socially vulnerable population, transgender people face numerous disparities in accessing health care. Most common difficulties are due to structural (related to systemic disadvantages) and interpersonal (reflecting negative personal attitudes) barriers within the health care context[14]. Firstly, there is a lack of health professionals who are specialized in providing gender-affirming care, whilst others may not be willing to treat transgender persons[15]. Secondly, trans individuals are often denied health insurance either for procedures that are routinely covered for their cisgender peers or for hormonal treatment and surgical sex reassignment. Low personal income further aggravates the lack of access to health services[16]. Thirdly, discriminative attitudes on the part of health personnel may lead transgender persons to postpone or even avoid seeking care[17].

The pandemic created unprecedented difficulties for trans persons both in attaining physical and social well-being and in accessing health care. The socio-economic circumstances of the coronavirus disease 19 (COVID-19) outbreak disproportionately affected transgender people in comparison with the general population. Increased unemployment rate and lower available income impeded access to both basic and expert clinical care[18]. Restricted access to mental health care and social support resulted in a loss of emotional resilience against the effects of gender-minority stress[19]. Although the latest variants of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are less pathogenic, the pandemic is still present and continues to fuel deficiencies in caring for trans people.

Gender-affirming care requires ongoing medical support for assessment, modification, and monitoring of the transition process. However, restrictive policies during the pandemic led most hospitals to cancel or postpone elective procedures (such as routine consultations and scheduled surgeries) in order to give priority to the management of COVID-19 cases. Thus, the accessibility to hormonal therapy and surgical sex reassignment became more difficult[20]. Shortages of medications also occurred[21]. These conditions arrested or hindered gender-transition for many trans persons and caused psychological distress due to the regression to undesired sex features[22]. Despite the withdrawal of most restrictive measures, much effort is still needed to normalize the situation.

LIVER FUNCTION IN TRANSGENDER MALES

The administration of testosterone is the typical masculinizing treatment in trans men[23]. There are certain modifications of the testosterone molecule which maintain or even enhance its virilizing effects but change its pharmacodynamic properties (Figure 1). The C-17α alkylation permits the oral administration of the substance by inhibiting its metabolic deactivation in the liver. The C-17β esterification (such as in testosterone enanthate, cypionate, and undecanoate) increases the potency and duration of action, but it requires a parenteral administration. However, the C-17α alkylated androgenic steroids have been implicated in causing liver damage, including prolonged cholestasis, hepatic peliosis, nodular regenerative hyperplasia, hepatic adenomas, and hepatocellular carcinoma. In contrast, the C-17β esterified molecules rarely cause cholestasis, but their prolonged use may increase the risk of hepatic tumors and nodular transformation, seemingly at a lower rate in comparison with the C-17α alkylated products[24]. Figure 2 presents the molecular structure of the most commonly used injectable preparations of testosterone in gender-affirming treatment.

C-17α alkylated derivatives of testosterone are not recommended for hormonal treatment of transgender males and thus, serious hepatic toxicity from oral pharmaceutical forms is usually avoided. Nonetheless, hepatotoxicity due to the long-term administration of exogenous testosterone esters is always a concern during therapy of transgender males. For this reason, trans men under androgen therapy should be monitored every three months during the first year of treatment and then semi-annually or annually[25]. Aspartate and alanine aminotransferases (AST and ALT, respectively) are the most commonly used biomarkers of liver injury. These enzymes catalyze the conversion of α-ketoglutarate and an amino acid to glutamate and another product[26]. The initiation of masculinizing gender-affirming treatment is expected to induce a slight increase in the blood levels of both AST and ALT. However, the clinical significance of these changes is usually minimal[27].

Testosterone acts through binding to the intracellular androgen receptors. This ligand binding results in conformational changes which in turn cause the translocation of the testosterone/receptor complex to the nucleus. There, it dimerizes and binds to androgen response elements on DNA, modulating thereby the transcription of specific genes that are important in cell development[28]. The mechanisms of the hepatotoxic effects of exogenous testosterone remain unclear. An impairment of cellular growth processes and an increase in oxidative stress within hepatocytes – both mediated by androgen receptors – are possible causes of liver damage related to the use of pharmaceutical forms of testosterone[29]. The etiology of cholestasis caused by testosterone derivatives is even more vague. It may be due to a disruption of the microfilaments within the hepatocytes that reduces their ability to transport bile[30].

Transmasculine gender-affirming therapy usually has no adverse effects on hepatic function[31]. Exogenous testosterone may cause minor serum enzyme elevations, but profound cholestasis, hepatic peliosis, and benign and malignant liver tumors are only theoretical risks. However, caution is

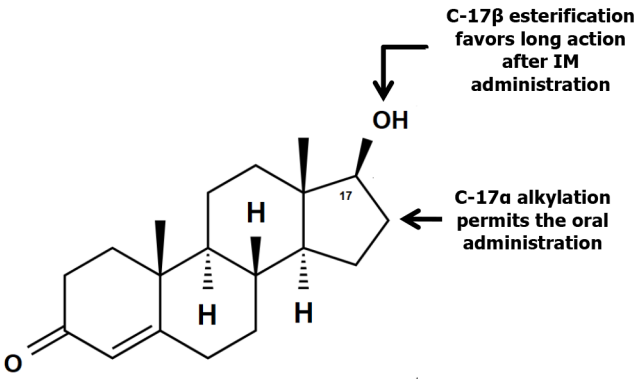

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Figure 1 The testosterone molecule - substitution at C-17 favors oral administration or long duration of action.

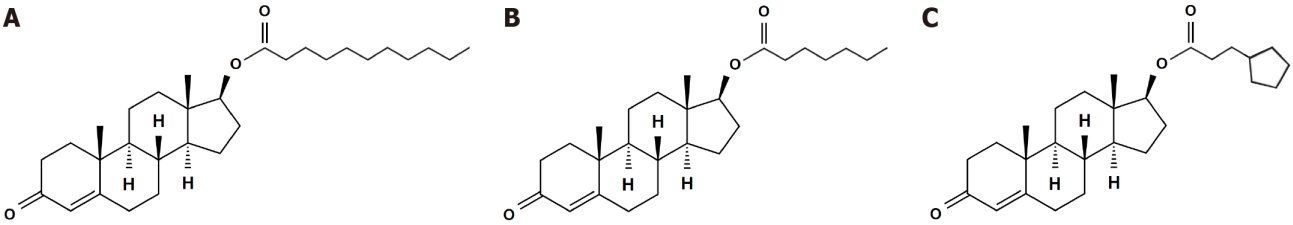

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Figure 2 Injectable testosterone semi-synthetic analogues. A: Undecanoate; B: Enanthate; C: Cypionate.

necessary when administering masculinizing treatment to patients with pre-existing liver disease due to the risk of deterioration of hepatic function. The principal step in managing potential liver damage is the pause of the administration of the androgenic steroid. Although some trans men may be disappointed with this decision, it is important to proceed to this action. Merely decreasing the dose of testosterone or switching to another formulation is not appropriate. Hepatotoxicity is usually reversible with the cessation of therapy, but full recovery often needs an extended period of time.

LIVER FUNCTION IN TRANSGENDER FEMALES

Transgender women are routinely treated with estradiol agents combined with anti-androgens or GnRH agonists if testes are present. The administration of estrogens has been rarely associated with liver disease at the dosages that are nowadays used either for contraception in cisgender females or for hormonal replacement treatment of postmenopausal women. Intrahepatic complications are more common with high doses of estrogens which is not a routine practice in gender-transition of trans females. Nevertheless, treatment with estrogens has been linked to susceptibility to venous thrombosis because of alterations in the hepatic synthesis of coagulation factors and antithrombin III. The risk is markedly greater with oral treatment because the intestinal absorption is rapid and yields high concentrations of hormone in the portal circulation[32]. Moreover, estrogens can cause a decrease in bile flow leading to intrahepatic cholestasis with pruritus and jaundice[33]. They may also be involved in the occurrence of nodular hyperplasia and hepatic benign and malignant tumors after long-term use, although the relevant evidence is not strong[34].

Exogenous estrogens, administered either orally or transdermally, induce physiologic processes that favor the formation of gallstones. Most clinical evidence derives from studies investigating the use of oral contraception or hormonal replacement therapy in cis women and the administration of estrogens for the treatment of prostate cancer in cis men. Accordingly, estrogen regimens are expected to increase the propensity of adverse biliary tract outcomes also in trans women receiving gender-affirming treatment. Indeed, therapy with exogenous estrogens can decrease nucleation time, enhance cholesterol saturation, and raise the biliary levels of arachidonate and prostaglandin E2. These effects are important risk factors which may result in cholelithiasis[35].

Cyproterone acetate is a steroidal anti-androgen that is routinely used in gender-transition of trans women. It inhibits the action of endogenous testosterone through blocking the androgen receptors. However, treatment with cyproterone acetate has been linked to liver-related adverse reactions. Most

cases appertain to modest and transient serum enzyme elevations. Nevertheless, instances of overt hepatotoxicity have been reported. The clinical features of hepatic injury may range from mildly symptomatic hepatitis with jaundice to acute liver failure. The relevant data have emerged mainly from studies of cis men receiving cyproterone acetate for advanced prostate cancer[36]. The relevant mechanism that leads to the liver damage is not clear. It is presumably an idiosyncratic reaction to the drug or its metabolites or an immunologically mediated response[37]. Occasional reports of hepatic cirrhosis and hepatocellular carcinoma induced by cyproterone acetate have also emerged[38]. In contrast, GnRH agonists (also used for suppression of gonadal testosterone) have not been implicated in causing clinically significant hepatotoxicity.

THE EFFECTS OF COVID-19 ON THE LIVER

SARS-CoV-2 is the etiological agent that causes COVID-19. The respiratory tract is the main target site of SARS-CoV-2 infection, but dissemination and replication of the pathogen in several other tissues can also contribute to the clinical impact of COVID-19. Hepatic tissue is a frequent site of extrapulmonary involvement of SARS-CoV-2. The incidence of liver injury in patients with COVID-19 ranges between 15% and 53%, although these figures may be different with the new variants of the pathogen[39,40]. Most common clinical features of liver dysfunction in COVID-19 are non-specific and may include fever, fatigue, anorexia, nausea, vomiting, diarrhea, and abdominal pain. Jaundice may also occur in rare cases. The laboratory findings of liver injury in COVID-19 include various degrees of ALT and AST elevations often combined with hypoalbuminemia and hyperbilirubinemia. In patients with COVID-19, abnormal liver function tests are associated with a greater risk of transfer to the intensive care unit, mechanical ventilator support, and mortality. As with other chronic diseases, prognosis from infection with the novel coronavirus is worse in patients with pre-existing hepatic disease (viral hepatitis, fatty liver, cirrhosis, hepatoma)[41].

SARS-CoV-2 enters the host cells through the membrane bound angiotensin-converting enzyme 2 (ACE2) receptor. The spike glycoprotein of the virion is composed of S1 and S2 subunits and protrudes from the viral surface. Upon binding to ACE2, the S1 subunit is dissociated with the ACE2 receptor with the presence of transmembrane serine protease 2 (TMPRSS2). This process results in conformational changes that increase the stability of S2 subunit and permit the viral envelope-cellular membrane fusion [42]. The respiratory tract is not the unique tropism for SARS-CoV-2. In humans, ACE2 and TMPRSS2 are present in multiple extrapulmonary tissues. In particular, ACE2 is highly expressed in cholangiocytes and to a lesser degree in hepatocytes, whilst TMPRSS2 is also expressed in both the hepatocytes and cholangiocytes[43]. The hepatic presence of these proteins renders the liver an accessible organ to SARS-CoV-2.

Pathogenesis in liver injury from COVID-19 is probably due to various mechanisms[39,40]. Firstly, direct viral cytopathogenic insult of hepatocytes and cholangiocytes may cause hepatobiliary damage. Secondly, the hyperinflammatory response induced by the viral infection and the accompanying hypercytokinemia may cause tissue damage and organ failure, especially in the liver. Thirdly, hepatotoxicity could derive from the variety of antiviral drugs, corticosteroids, antibiotics, and antipyretics that are used for treatment of COVID-19 patients. Fourthly, hypercoagulable state associated with COVID-19 and the resultant thrombosis may cause hepatic degeneration[44]. Lastly, cardiac and respiratory failure may lead to circulatory compromise, causing thereby a hypoxic injury to the liver[45,46]. Nevertheless, several other underlying mechanisms may contribute to liver injury in COVID-19 patients. Moreover, the pathophysiological synergy of pre-existing liver disease and COVID-19 is possible and needs to be thoroughly evaluated.

MONITORING TRANSGENDER LIVER FUNCTION IN THE ERA OF THE PANDEMIC

Currently, transgender people constitute a non-negligible percentage of the general population. Hormonal therapy is an essential component of gender-affirming treatment because it can lead to improvements in psychological functioning and quality of life among the recipients[47]. However, hepatotoxicity is a major concern with the long-term administration of either testosterone derivatives or oral estradiol and anti-androgens. The incidence of drug induced liver injury due to usual transmasculine and transfeminine hormonal regimens is seemingly low[48,49]. Nevertheless, monitoring of liver function on a regular basis is important[50] because of the severity of the potential hepatic impairment from gender-affirming pharmacotherapies and possible liver comorbidities among trans people. This strategy can assist in the prevention of therapeutic failures and in the avoidance of adverse side effects [51].

Protecting liver integrity of transgender people becomes even more crucial in case of a SARS-CoV-2 infection. In general, the interplay of immune mediators and drugs with hepatotoxic properties could synergistically increase the toxic effect on liver[52,53], although relevant evidence does not exist for trans patients with COVID-19. Furthermore, almost all the drugs prescribed for both the COVID-19

management and the cross-sex hormonal treatment are metabolized in the liver, hence an elevation of hepatic enzymes and possible drug induced liver damage due to a cumulative effect is expectable[54].

For the aforementioned reasons, special consideration should be paid to minimize the risk of hepatic damage from COVID-19 in these patients. For this purpose, assessment of trans persons with SARS-CoV-2 infection should include a thorough evaluation of hepatic function in addition to the investigation of primary respiratory manifestations. Furthermore, appropriate care with continuous laboratory monitoring, clinical observation and, if needed, specific treatment is significant, especially in cases of hospitalization. Liver function tests should be regularly observed, and viral hepatitis markers should be determined. Imaging studies of the liver, gallbladder, and biliary tract should be performed in case of abnormal laboratory findings. Cautious utilization of pharmacotherapies is also necessary. Gender-affirming hormonal treatment is not a contraindication of vaccination against COVID-19. Thus, transgender people should be advised to get vaccinated with initial and booster doses according to the general recommendations.

CONCLUSION

Although gender-transition *per* se does not imply a worse prognosis in COVID-19, prior vulnerabilities with regards to health problems and the impaired access to health care of trans people were exacerbated by the pandemic. Adverse hepatotoxic effects of cross-sex hormonal therapy, although uncommon in daily practice, become particularly important in case of SARS-CoV-2 infection. The possible synergistic impact of COVID-19 on liver both in the short- and in the long-term must not be neglected and requires proper investigation and management. A multicentric study may contribute to a deeper knowledge about this issue. The pandemic can be an opportunity to provide equal access to care for all and increase the resilience of the transgender population.

FOOTNOTES

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MINIREVIEWS

Telenutrition for the management of inflammatory bowel disease: Benefits, limits, and future perspectives

Merve Güney Coşkun, Ezgi Kolay, Metin Basaranoglu

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Abstract

Patients with inflammatory bowel disease (IBD) require lifelong and personalized care by a multidisciplinary healthcare team. However, the traditional medical model is not ideal for patients who require continuous close monitoring and whose symptoms may dramatically worsen between regularly scheduled visits. Additionally, close dietary follow-up and monitoring of IBD in a traditional setting are challenging because of the disease complexity, high pressure on outpatient clinics with a small number of IBD specialist dietitians, and rising incidence. Given the significant burden of IBD, there is a need to develop effective dietary management strategies. The coronavirus disease 2019 pandemic caused an unprecedented shift from in-person care to delivering health care *via* technological remote devices. Traditional nutrition therapy and consultation can be provided by telenutrition through remote electronic communication applications that could greatly benefit patient care. Telenutrition might be useful, safe, and cost-effective compared with standard care. It is likely that virtual care for chronic diseases including IBD will continue in some form into the future. This review article summarizes the evidence about telenutrition applications in the management of IBD patients, and we gave an overview of the acceptance and impact of these interventions on health outcomes.

Key Words: Telenutrition; Telemedicine; Digital health; Inflammatory bowel disease; Symptom monitoring; Self-management

Core Tip: Routine nutritional assessment, education, and close communication about diet are essential for professionally recommended diets, and they are a potential therapeutic strategy for inflammatory bowel disease onset and severity. Traditional nutrition therapy and consultation can be provided by telenutrition through remote electronic communication applications, which could greatly benefit patient care. Telenutrition is a self-management tool offering cost-effective, quick, and accessible personalized dietary advice for inflammatory bowel disease patients that require lifelong follow-up and maintenance treatment. However, there are certain barriers to legacies, education, sufficient equipment, and privacy. Further studies and interventions should focus on removing barriers while improving benefits.

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INTRODUCTION

Traditional inflammatory bowel disease care

Inflammatory bowel disease (IBD) is a relapsing disease manifested by focal asymmetric, transmural, and granulomatous inflammation, which includes ulcerative colitis and Crohn's disease[1]. Ethnic origin, genetics, gut microbiome, environmental factors, immune response, and lifestyle are the main factors in the epidemiology of this disease[2]. The incidence IBD has increased from 0.5% in 2010 to 0.75% in 2020, and it is expected to rise to > 1% of the population by 2030[3]. This will result in a high demand for health care worldwide[4,5]. IBD is characterized by active disease (flares), remission periods, and symptoms that may dramatically worsen between regularly scheduled visits. Inadequate clinical management might result in irreversible intestinal fibrosis and even cancer[6-8].

Diet is considered a potential therapeutic strategy for IBD onset and severity. IBD specified nutrition care could have an anti-inflammatory effect, regulate the immune system, support the mucous layer, contribute to microbial healing, and other mechanisms. The International Organization for the Study of IBD revealed dietary guidance based on the best current evidence[9]. Dietary recommendations include regular intake of fruits and vegetables (in remission) and reduce saturated, trans, and dairy fat intake for patients with Crohn's disease. The dietary practice focuses on increasing the consumption of natural sources of omega-3 fatty acids while decreasing the consumption of saturated, trans, dairy fat, and red and processed meat for patients with ulcerative colitis[9]. Although several dietary patterns (such as the Mediterranean diet, specific carbohydrate diet, and Crohn's disease exclusion diet) are commonly recommended for patients with IBD, a personalized approach and close monitoring are the key to successful nutritional support[10-12]. Additionally, diet recommendations and characteristics of the diet may differ depending on whether the patient's disease is acute or in remission, the medication type, perianal abscess fistula if stricture development is present, and pre- and post-operative status[9,13].

On the other hand, malnutrition and body mass index of people with obesity are predictive factors for IBD[2]. In order to determine unintentional weight loss, rapid weight gain, and nutritional deficiencies, nutrition consultation should be provided as early-stage dietetic support[14]. Furthermore, close dietary follow-up and monitoring of IBD in a traditional setting are challenging due to the disease complexity, the limited number of IBD specialist dietitians in outpatient clinics, and rising disease incidence. The British Society of Gastroenterology consensus guidelines suggests that 0.5 whole-time equivalent dietitians should be allocated to gastroenterology per population of 250000[15]. Along with that, IBD patients require continuous, close, and personalized monitoring to minimize short-term and long-term undesirable outcomes. However, the traditional medical model for IBD care may not be ideal for patients who require lifelong and personalized care by a multidisciplinary healthcare team (gastroenterologists, surgeons, nurse practitioners, psychologists, and dietitians).

The traditional medical model for IBD offers a routine follow-up visit depending on disease history, phenotype, activity, and current treatment, including regular disease monitoring tests (clinical, biochemical, stool, endoscopic, cross-sectional imaging, and histological investigations)[2]. The clinical follow-up timeline given by the ECCO-ESGAR Guideline recommends that in patients with IBD who have reached clinical and biochemical remission, monitoring ensures early recognition of the disease flare[2]. The interval of monitoring should be between 3-6 mo depending upon the duration of remission and current therapy. Moreover, endoscopic surveillance should be performed to detect changes from 1-5 years depending on risk factors[2]. Therefore, this study aimed to review the literature on the benefits and limits of telenutrition in IBD nutrition care and provide future perspectives to

improve telenutrition applications.

Transition to telemedicine and telenutrition in IBD

In broad terms, telemedicine can be defined as the transfer of health resources and health care in distance conditions. The telemedicine term embodies many concepts that cover telemonitoring, tele-education, teleconsultation, and telecare as well as m-health[16]. According to a definition provided by The American Telemedicine Association, it also aims to improve a patient's clinical health status[17]. The transformation of IBD care is rapidly rising after coronavirus disease 2019 (COVID-19) through novel approaches to telemedicine with targeting convenient access and well-tolerated IBD care. The ECCO Position Statement on IBD management during the COVID-19 outbreak recommended implementing telemedicine, monitoring at distance, reporting outcomes online, promoting local labs with e-mail reports, implementing point-of-care biomarkers, calprotectin measurement at home, and measurement of drug levels (therapeutic drug monitoring) with rapid tests[2].

On the other hand, most of the IBD patients experienced psychological distress and were inadequately informed about the management of their chronic condition during the COVID-19 pandemic[18,19]. A vital issue is considering the psychological well-being of the patients, detecting vulnerable groups *via* various questionnaires, and preventing stigmatization during the consultation[20-22]. Therefore, switching to telemedicine as an alternative first-choice follow-up tool supporting therapeutic adherence is highly recommended after the pandemic.

Given the significant burden of IBD, there is a need to develop effective dietary management strategies. Traditional nutrition therapy and consultation can be provided by telenutrition through remote electronic communication applications that could greatly benefit patient care. Telenutrition is one of the major components of telemedicine, and the Academy of Nutrition and Dietetics characterized it as virtual dietary consultations including telecommunications technologies to apply the Nutrition Care Process[23]. In recent years, there has been an increasing interest in telenutrition applications for the long-term monitoring and nutrition management of chronic diseases[24]. A growing body of literature follows this statement: Telenutrition is becoming a suggested strategy to overcome barriers and increase access to nutrition care[25]. Consequently, the transition to telenutrition practices in IBD can be promising to overcome the barriers and challenges that arise in the nutrition care of the disease.

Techniques and applications of telenutrition in IBD

Telemedicine is most frequently transmitted through the internet *via* high-quality web portals, online courses, smartphone applications, or telephone[26]. Telenutrition modules can implement applications to complete IBD patient care. Dietitians who specialized in IBD could also be involved in applying and operating most telemedicine interventions and projects. Routine nutritional assessment, education, and close communication about diet are essential for professionally recommended diet and dietary restrictions to control symptoms, and long-term monitoring of behaviors that may trigger symptoms [27]. Additionally, various factors and nutritional factors can affect patient health and quality of life[28]. Therefore, telenutrition as a communication method could be considered to meet individual patients' requests. A comprehensive medical history of IBD patients should be recorded at the first consultation. Assessment tools are also useful for ensuring a consistent approach and can be used by dietitians during initial and follow-up telenutrition visits. Validated tools for objective measures include the IBD questionnaire[29], which is considered the gold standard for use in clinical trials, food-related quality of life[30], Subjective Global Assessment, the Malnutrition Universal Screening Tool, Malnutrition Inflammation Risk Tool, Saskatchewan IBD Nutrition Risk Tool, and Nutrition Risk Screening 2002[31] and could be appropriate and useful in certain situations. Monitoring and identifying psychological dimensions that could affect the clinical course of the disease with various approaches would be useful in determining the psychological effects of nutrition[32]. Additionally, micronutrient deficiencies should be assessed in the beginning and reassessed as needed. Deficits can occur even in apparently well-nourished patients or in patients without laboratory results[33]. Patients on elimination diets, who present with symptoms of deficiency or who meet < 75% of estimated energy requirements for > 1 mo should be monitored closely. Last but not least nutritional education must be included in telenutrition consultations. Figure 1 summarized the telenutrition in IBD care with medical and dietary considerations, which can be implemented in the first consultation and long-term monitoring of IBD patients.

Benefits and limits of telenutrition in IBD care

The benefits of telemedicine can be listed under several headings: access and monitoring; cost-effectiveness; information sharing; and communication between health professionals and patients[34]. An umbrella review that investigated the clinical effectiveness of telemedicine revealed that it can positively affect diet and lifestyle-related factors such as improvement in glycemic control in diabetic patients, helping patients increase physical activity, and improving diet quality and nutrition[35]. Telemedicine technology enhances the accessibility of medical data and healthcare professional monitoring of patients [34]. Accessibility to telehealth applications including telenutrition has grown rapidly during the COVID-19 pandemic time due to contact limitations[36]. The results from a survey study conducted in Italy demonstrated that after the COVID-19 pandemic, the accessibility of telenutrition increased from

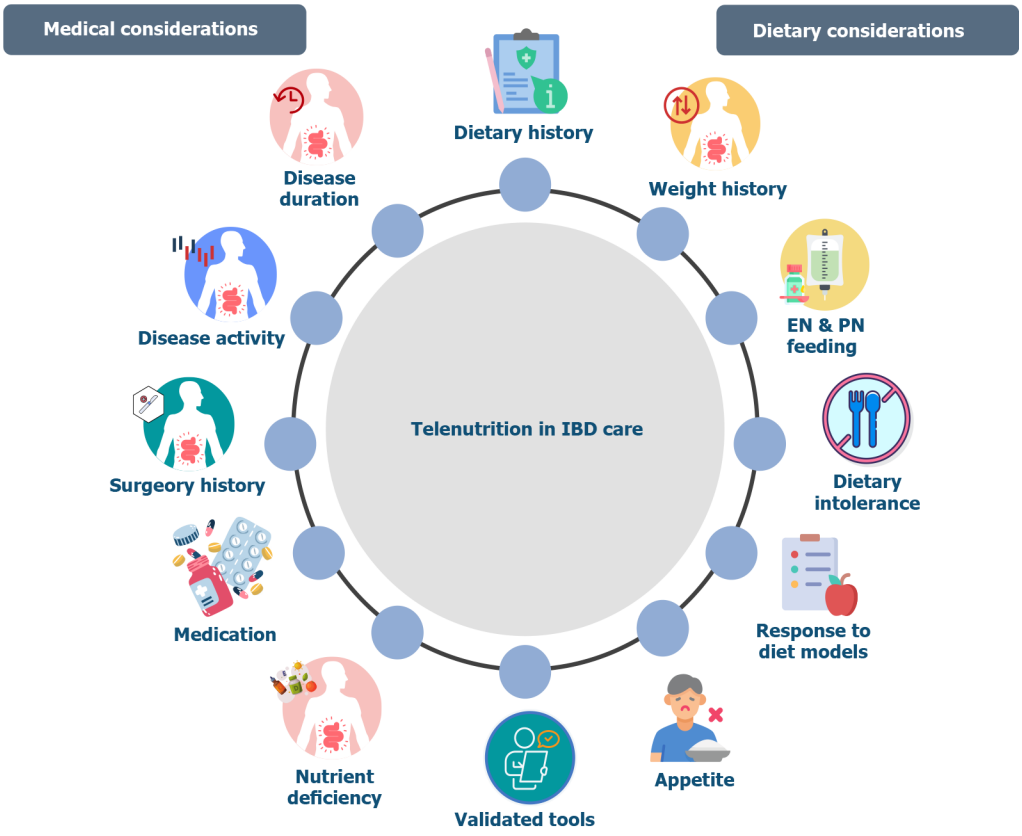

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Figure 1 Telenutrition in inflammatory bowel disease care for first consultation and long-term monitoring. The first telenutrition consultation for inflammatory bowel disease (IBD) patients includes: (1) Age at diagnosis; (2) Extent and duration of disease; (3) History of surgical procedures; (4) Current and past medications; (5) Current disease activity; (6) Health behaviors (*e.g.*, smoking and alcohol consumption); (7) Current and past enteral or parenteral feeding history; (8) Dietary history; (9) Dietary triggers or intolerance; (10) Appetite; (11) Nausea, vomiting; (12) Weight history; (13) Complementary and alternative medicine usage; (14) Response to or adverse effects of any previous diet model; (15) Micronutrient deficiencies; and (16) Validated tools for certain situations (*e.g.*, food-related quality of life, Subjective Global Assessment, Malnutrition Universal Screening Tool, Malnutrition Inflammation Risk Tool, Saskatchewan IBD Nutrition Risk Tool, and Nutrition Risk Screening 2002). Long-term monitoring of inflammatory bowel disease patients includes: (1) Evaluating adherence to diet treatment should be a part of each virtual appointment; (2) 7-d diet diary (3-d minimum); (3) Current medications; (4) Current disease activity; (5) Appetite; (6) Nausea, vomiting; (7) Any changes in dietary habits (new dietary triggers, intolerance, or complementary and alternative medicine usage; (8) Weight; and (9) Repeat testing of validated tools for certain situations. EN: Enteral nutrition; PN: Parenteral nutrition.

16% to 63%[37]. Australia's study on reimbursed telehealth dietetics services showed that telehealth items for dietitians have increased by 17.7% and represent 5% of total dietetics services provided by telemedicine[38].

Moreover, financial burdens and difficulties can be considered key barriers for patients with IBD to obtain healthcare services[39]. Existing research recognizes the financial contribution of telehealth considering the importance of cost-effectiveness and cost-saving in the healthcare system. Collective data supported the economic benefits of m-health usage compared to traditional applications[40]. These results seem to be consistent with other research that found videoconferencing can be cost-saving and highly effective for patients with IBD[41]. It is important to consider that the majority of studies investigate telehealth rather than telenutrition. Although the results obtained from telehealth studies can be extrapolated to telenutrition, it should be noted that diet-related factors may affect the outcomes. The improvement in telehealth technologies is unlikely to cause significant increases in cost or access and will assist the population to support a healthier diet to fight against chronic disease outcomes.

Telemedicine is particularly beneficial for IBD patients for treatment management, education, self-reported disease activity, and outcomes[42]. A recent review reported mixed results when comparing face-to-face visits with telemedicine visits[42]. Most IBD-related apps allow patients to record symptoms, bowel habits, and dietary history to log meals, nutrition, medications, and mood[43-45]. Telemedicine systems become prominent in being safe, feasible, cost-effective, meeting patients' needs, and overcoming distance barriers between patients and healthcare facilities[44]. Several telemedicine systems for IBD patients that provide nutritional support are listed in Table 1.

In spite of all mentioned benefits of telemedicine, there are certain limitations that are necessary to consider. The most important limitations are legal and ethical issues including privacy protection, difficulties with equipment, educating patients and health professionals in the usage of telenutrition, patient-centered barriers, and financial sources spent on system adjustments[51,52]. Telemedicine

Table 1 Summary of the most relevant telemedicine systems with nutritional support for inflammatory bowel disease patients

Ref.	Study/application	Country	Design	*n*	Benefits for nutritional aspects
Habashi *et al*[46], 2019	Promoting access and care through centers of excellence	Canada	Prospective comparative study	90 patients with IBD	Including IBD nutrition expert in the health care team. Providing frequent consultations, reducing wait times and cost savings
Ehrlich *et al*[47], 2012	GI buddy	Crohn's and Colitis Foundation	Application	N/A	Allowing patients to record their symptoms, bowel movements, diet, physical activity, and medication adherence, notes, questions, or doubts for the next clinician interaction. Helping patients and healthcare team see how IBD may be affecting patients, improving IBD management and quality of life
Oshi Health [48], 2022	Oshi Health	United States	Application	N/A	Providing nutrition and dietary support, health coaching, IBD-friendly recipes, provides a space to message with professionals, symptom tracking
de Jong *et al*[49], 2017	myIBDcoach	Netherlands	Randomized controlled trial	909 patients with IBD (n = 465 telemedicine, n = 444 standard care)	Providing eLearning modules about medications, adherence, smoking cessation, nutrition, symptom management, fatigue, work productivity, anxiety, and depression. Showing plan and messaging care team, weekly or monthly assessment (monitor IBD at home questionnaire) according to disease severity
Gupta *et al*[50], 2022	IBD NutriCare	India	Prospective observational study	49 patients with IBD	Recording daily diet and other disease-related parameters to provide timely telenutrition counselling, comprehensive analysis report including nutrient intake, calorie distribution of patient's daily intake, and weight records, giving answers, frequently asked questions about diet in IBD, sending notifications or message from the dietitians

IBD: Inflammatory bowel disease; N/A: Not applicable.

systems may not be appropriate for patients who do not have well-established treatment plans. Furthermore, patients may not be familiar with the technological applications or must invest extensive time to become familiar. Also, it must be underlined that studies were mainly conducted in developed countries, and there might be differences in terms of equipment quality and internet availability in some countries[40]. Telemedicine settings in low and low-middle income countries may be limited by financial elements and interference with the cost-effectiveness[40]. Besides the financial barrier, careful consideration must be given to patient privacy and data protection. There is a need for further improvement from both the clinical dietetic practice and patient perspective. Even though the results of limited study samples cannot be generalized, evidence shows that telenutrition has a significant impact on patient education, treatment adherence, medication management, quality of life, and care[42].

Besides limitations related to telemedicine, nutrition-specific barriers must be recognized in overcoming possible obstacles. Considering that anthropometric measurements are essential components of nutritional assessments, self-reported weight and height bias must be addressed as a limitation of telenutrition[40].

CONCLUSION

Digital health interventions and self-monitoring offer quick, cost-effective, personalized, accessible medical care and nutritional advice[53]. Especially when considering the rising number of IBD patients and an insufficient number of specialists, telemedicine could reduce the burden on the healthcare system by providing digital sources. Patients with less aggressive disease severity or in remission can likewise be followed up *via* telenutrition applications supported by a dietitian. However, studies showed some barriers, and it is not yet proven if telemedicine monitoring can change the natural disease course of IBD. Future studies with larger sample sizes are needed to evaluate the telenutrition side of digital health interventions in the following areas: (1) Nutritional assessment accuracy, dietary model acceptability, telenutrition effectiveness, and self-management of dietary triggers; (2) Dietary recommendations through artificial intelligence need proper validation and investigation of their clinical utility in real-life settings before recommending clinical use; (3) More ease-of-use virtual interface adaptations are needed for delivering telenutrition for dietitians and populations including the elderly or with limited digital literacy; and (4) Standard telenutrition care procedure need to be established and include data protection systems to ensure patient privacy and security[54].

FOOTNOTES

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MINIREVIEWS

Liver transplantation amidst the COVID-19 era: Our center's experience

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Abstract

Coronavirus disease 2019 significantly impacted the liver transplant process worldwide. Consequently, it brought significant challenges and limitations to transplant policies and organ allocation forcing liver transplant centers to adjust their protocols to ensure maximum benefit and avoid harm to their patients. Our center, like many others, was obliged to adapt to the challenges. This paper provided an overview of the effects of coronavirus disease 2019 on liver transplantations and detailed our center's experience and efforts during this unprecedented pandemic to serve as a guide for future public health crises.

Key Words: COVID-19; Liver transplantation; Immunosuppression; Experience; Mortality

Core Tip: The coronavirus disease 2019 pandemic gave rise to an exceptional situation for liver transplantation (LT) around the world, initially leading to a decline in LT followed by a rapid recovery. This robust response resulted from extensive efforts by various LT centers to offset these challenges in addition to emerging evidence and the provision of appropriate guidelines from major LT societies. It is of the utmost importance to share experiences among LT centers to improve outcomes and reduce graft loss.

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INTRODUCTION

The coronavirus (COVID-19) pandemic represented an unforeseen crisis to healthcare systems and transplant centers around the world, resulting in significant changes to solid organ transplant (SOT) practices[1,2]. At the beginning of the pandemic, a decrease in SOT was observed and attributed to multiple factors, which included a shortage of resources and staff, a saturation of critical care beds, changes to the donor pool, and uncertainty regarding optimal post-transplant immunosuppressive therapy. The stress on the health care system forced most of the transplant centers to reduce liver transplant (LT) activity to best utilize scarce resources.

LT centers that continued their activity had to adjust their policies and develop strategies that ensured the safety of their patients, including protocols regarding testing of donors and candidates, reorganization of clinical and isolation protocols to establish a coronavirus-free pathway, rearrangement of the waitlist based on priority, and promotion of telemedicine to minimize exposure to the virus[3-5]. The United States was not the exception, and the initial reduction in the number of LT performed at the beginning of 2020 was followed by a brisk comeback in the second half of 2020 and early 2021. The emergence of evidence and recommendations by the international transplant societies was crucial in guiding LT programs during these unprecedented times[6].

In this article, we discussed our center's experience with COVID-19 regarding its effects on LT patients, including the pretransplant, perioperative and post-transplant periods.

COVID-19 EFFECTS ON LT VOLUME AT OUR CENTER

Soon after the pandemic was declared we observed a decline in the number of LT performed at our center, which was similar to other LT centers across the nation[7]. From March 2020 to February 2021, 42 LT were performed, representing a reduction of 14.28% of the cases when compared to the same period 1 year earlier. Subsequently, from March 2021 to February 2022, a 38.77% decrease in LT was noted when compared to the period between March 2019 and February 2020 and a reduction of 28.57% when compared to the period between March 2020 and February 2021 (Figure 1).

COVID-19-RELATED LT CONSIDERATIONS

Prevention

General COVID-19 preventive measures for LT candidates are similar to those established for the general public. We continue to recommend that LT recipients maintain personal measures to minimize exposure to COVID-19, such as social distancing, masking, and avoiding gatherings whenever possible, regardless of vaccination status.

LT centers faced significant ethical challenges of vaccine skepticism and uncertainty regarding if it should be mandatory for all candidates on the waitlist[8]. Based on guidance from international transplant societies, vaccination against COVID-19 was strongly recommended for patients with chronic liver disease[9]. However, SOT recipients were found to mount a lower humoral response to COVID-19 vaccination, for which the administration of booster doses was deemed necessary to achieve acceptable immunity[10,11].

On August 12th, 2021, the Food and Drug Administration approved a three-dose mRNA vaccine series for immunocompromised patients, including SOT recipients[12]. In addition, the Advisory Committee on Immunization Practices recommended that all immunocompromised adults should be vaccinated at least 3 mo after the third inoculation of the mRNA vaccine or 2 mo after the initial sequence of the Johnson and Johnson vaccine[13]. We agree with these recommendations, and in our

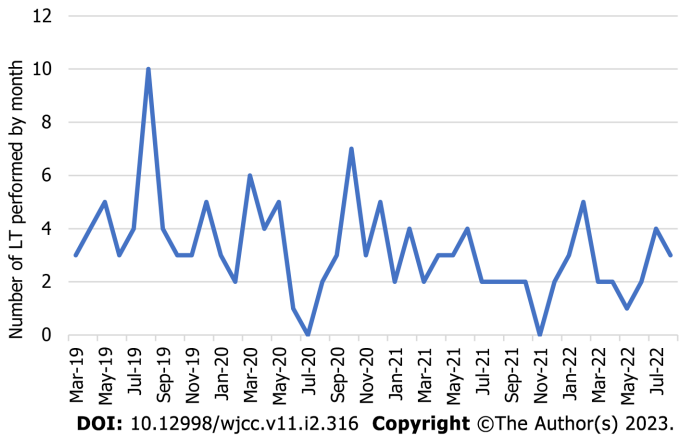

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Figure 1 Number of liver transplants performed per month in our center between March 2019 and July 2022. LT: Liver transplant.

center we highly recommend that all patients listed for LT receive at least three doses of an mRNA vaccine before transplant.

At the beginning of 2022, the Food and Drug Administration published an Emergency Use Authorization for tixagevimab/cilgavimab (Evusheld), a long-acting monoclonal antibody for pre-exposure prophylaxis of COVID-19 in patients with moderate to severe immunosuppression[14]. Evusheld became an attractive armamentarium for protection against COVID-19 infection in LT recipients who may not be able to mount an appropriate immune response to the vaccine[15]. In a retrospective study that followed 378 patients with hematologic malignancies, less than 60% of patients seroconverted after the third vaccine dose, regardless of the therapy used. Thirty-three patients (8.8%) eventually developed COVID-19 infection, and among them 3 patients died due to severe infection. Importantly, no deaths occurred among patients who achieved seroconversion, and none of the patients who received Evusheld (n = 25) developed COVID-19 infection[10]. Although data on the use of Evusheld may be lacking in the SOT population, at our center we adopted the use of Evusheld in all patients who undergo LT, irrespective of vaccination status.

COVID-19 in LT candidates

Early case reports from Korea and India studied the viability of conducting an LT after 14-28 d of a positive COVID-19 infection in asymptomatic or minimally symptomatic patients[16,17]. In addition, a retrospective multicenter study from 11 European countries reported 26 patients who received an LT after a median of 78.5 d from an initial positive test for COVID-19. Even though LT candidates with symptomatic COVID-19 were at higher risk of early mortality when compared to counterparts with similar Model for End-stage Liver Disease scores, those who underwent LT had a favorable short-term survival of 96%. This study showed that once patients recover from COVID-19, LT is safe and encouraged[18].

In our center, patients on the waitlist who have a positive PCR test for COVID-19 are temporarily inactivated until becoming asymptomatic and 3 wk have elapsed since their initial positive test. Subsequently, if the patient had respiratory symptoms, we perform a contrast-enhanced computed tomography of the chest and pulmonary function tests before waitlist reactivation. Conversely, if the patient did not develop any respiratory symptoms, they are reactivated without further testing.

Donor COVID-19 positivity

During the beginning of the pandemic, transplant societies recommended against SOT in situations where donors tested positive for COVID-19 due to the likelihood of developing complications, such as acute respiratory distress syndrome or thrombosis of the graft. However, as the pandemic continued, the Organ Procurement and Transplantation Network Ad Hoc Disease Transmission Advisory Committee recommended that the decision to transplant organs from donors with active infection of COVID-19 should take into consideration the likelihood of death of the recipient for delaying the procedure and the risk of transmission to members of the transplant team.

Nevertheless, studies revealed that, unlike lung transplant recipients, the chance of disseminating COVID-19 infection from the donor to the recipient was low in LT patients[19]. The degree of viral load in the blood is usually low, and therefore blood-borne transmission does not represent a significant risk [20]. In our center, we actively consider liver grafts from donors who are COVID-19 positive at the time of organ donation.

COVID-19 in LT recipients

Initial reports suggested that LT recipients could be at an increased risk of acquiring severe COVID-19,

given their immunosuppressed status, with the inherent risk of long-term viral shedding[21,22]. Although some studies showed an increased infection rate among SOT recipients, this was not associated with worse clinical outcomes. The Spanish Society for Liver Transplantation conducted a prospective nationwide study that included 111 LT recipients and concluded that these patients were twice as likely to be infected with COVID-19 compared to age- and sex-matched individuals (standardized incidence: 191.2; 95% confidence interval: 190.3-192.2)[23]. However, another prospective study from Italy followed 30 LT recipients with COVID-19 and suggested that LT recipients were more symptomatic yet with no increased risk of hospitalization or death[24].

The approach to management varies based on the severity of the COVID-19 infection and largely stems from experts' opinions. It is generally advised to lower the cumulative dose of immunosuppression, particularly mycophenolate mofetil, if possible[23]. Immunosuppression was found to be an independent predictor of severe COVID-19 disease as it may interfere with mounting a humoral response to COVID-19 vaccination[25]. Commonly used agents for outpatient management of COVID-19 infection include oral antivirals such as molnupiravir and nirmatrelvir/ritonavir (Paxlovid). Molnupiravir appears to be effective, safe, and well-tolerated in LT patients[26]. Nonetheless, Paxlovid strongly interacts with calcineurin inhibitors, so concomitant use is contraindicated due to the potential for calcineurin inhibitor toxicity[27]. For those requiring inpatient management of COVID-19, the nucleotide analog remdesivir is our preferred therapeutic option. It has been shown to shorten the duration of illness and hospitalization, especially when given to patients on supplemental oxygen within 10 d of symptom onset[28].

We also use COVID-19-specific antibodies in LT recipients with COVID-19, mainly in the outpatient setting and selected patients in the inpatient setting. In a single-center, retrospective study that included liver and kidney transplant recipients, COVID-19 monoclonal antibody (casirivimab-imdevimab or bamlanivimab) reduced hospitalization from 32% to 15% (P = 0.045) with no mortality (13% *vs* 0%, P = 0.04)[29].

Impact on LT medical staff

Healthcare providers are well-known to be at an additional risk of contracting COVID-19 when compared to the general population[30]. At our center, we adopted a strategy of decreasing interactions among team members to mitigate the risk of COVID-19 transmission. All meetings, including LT selection and multidisciplinary tumor boards, were transitioned to an online platform. A strict departmental protocol was implemented for caregivers who developed symptoms to allow them to undergo testing and appropriate isolation. Outpatient visits, when necessary, were shifted to an online platform to minimize unnecessary exposure and protect patients and staff members.

CONCLUSION

The COVID-19 pandemic has impacted transplant centers globally. Despite the burden, LT centers have been forced to adopt protocols to ensure patient and caregiver safety. A limitation of this review is that it only provides the experience of one LT center in the United States. In the future, emerging evidence will further guide LT centers toward the creation of contingency plans to provide optimal pretransplant, perioperative, and post-transplant care in future public health crises.

FOOTNOTES

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MINIREVIEWS

Prospects for the use of olfactory mucosa cells in bioprinting for the treatment of spinal cord injuries

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Abstract

The review focuses on the most important areas of cell therapy for spinal cord injuries. Olfactory mucosa cells are promising for transplantation. Obtaining these cells is safe for patients. The use of olfactory mucosa cells is effective in restoring motor function due to the remyelination and regeneration of axons after spinal cord injuries. These cells express neurotrophic factors that play an important role in the functional recovery of nerve tissue after spinal cord injuries. In addition, it is possible to increase the content of neurotrophic factors, at the site of injury, exogenously by the direct injection of neurotrophic factors or their delivery using gene therapy. The advantages of olfactory mucosa cells, in combination with neurotrophic factors, open up wide possibilities for their application in three-dimensional and four-dimensional bioprinting technology treating spinal cord injuries.

Key Words: Olfactory mucosa cells; Neurotrophic factors; Cell therapy; Injury of spinal cord; Three-dimensional bioprinting; Four-dimensional bioprinting

Core Tip: The development of an optimal strategy for the treatment of spinal cord injuries is a relevant and topical issue in modern medicine. Olfactory mucosa cells and neurotrophic factors showed their effectiveness in transplantation into the area of the injured spinal cord. In this review, the authors discuss the possibility of their application in four-dimensional bioprinting to create transplants that would have a complex impact on the transplant-mediated repair of the damaged area of the spinal cord.

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INTRODUCTION

Therapy for spinal cord injury is a relevant issue in modern neurobiology and medicine because the mechanical injury of the spinal cord can lead to irreversible changes in the neural tissue. Spinal cord injuries often lead to disabilities and sometimes can have a lethal outcome[1].

One of the current strategies for the treatment of spinal cord injury is cell therapy. The most optimal source of cells for transplantation may be olfactory mucosa cells. Obtaining olfactory cells is an atraumatic procedure for a patient, which makes the application of this tissue in therapy a promising field of study in personalised medicine. For cell transplantation of the olfactory mucosa cells, neural stem/progenitor cells (NSPCs), olfactory ensheathing cells (OECs), and mesenchymal stem cells (MSCs) are obtained. It was shown that the transplantation of these cells contributed to the reparation of the injured tissue of the spinal cord[2]. Besides, spinal cord therapy involves the application of various neurotrophic factors. Neurotrophins exert an antiapoptotic effect and contribute to the survival of mature neural cells, which is especially important at the site of injury[3]. The application of neurotrophins in combination with olfactory mucosa cells can enhance the therapeutic effect of these cells. This combination promotes cell survival, axonal regeneration, structural repair and function recovery after injury Table 1.

In the last few years, experimental medicine research included the application of various variants of stable polymers that can deliver cells and neurotrophic factors as a three-dimensional (3D) scaffold[4]. This method has shown its safety in various clinical studies[5,6]. The 3D scaffold provides support for the transplanted cells in more native conditions, which contributes to their survival in the area of injury [7,8]. However, such 3D scaffolds have low adaptivity to the changes in the area of injury and limited changes in shape. The solution to this problem is the development of conceptually novel "smart" materials. The application of such materials will allow specialists to create four-dimensional (4D) scaffolds that will not only combine the advantages of 3D scaffolds, but can also adapt to changes in the area of injury, and respond to external signals[9].

Thus, the creation of structures that have all the advantages of 4D bioprinting and can deliver olfactory mucosa cells and neurotrophic factors will be a breakthrough in the treatment of spinal cord injuries.

OLFACTORY MUCOSA CELLS IN THE TREATMENT OF SPINAL CORD INJURIES

The olfactory mucosa of the nose contains several cell types that can be successfully used in cell therapy for spinal cord injuries: NSPCs, ECs, and MSCs.

Despite the fact that cell-therapy based on olfactory mucosa cells is one of the most promising treatments for spinal cord injuries there are some limitations to this approach. Transplantation of OECs from olfactory mucosa significantly improves motor function recovery and reduces the size of cysts[10, 11]. However, there is a problem with OEC culture heterogeneity because it is currently difficult to purify these cells to a 100% pure culture, so there might be some side effects[12-14]. Mesenchymal stromal cells can also be obtained from olfactory mucosa. As it was mentioned in the manuscript, studies show that mesenchymal stromal cells transplantation has side effects such as neuropathic pain

Table 1 Effects of using olfactory mucosa cells with neurotrophins in spinal cord injuries

	BDNF	NT-3	NGF
NSPCs	Improved hindlimb function[75]	Promoted differentiation into neurons [76]; promoted axon regeneration and functional recovery[77]	Reduced oligodendrocyte loss, improved functional recovery, preservation of motor neurons, attenuation of astrocytosis[78]
OECs	Improved cell survival[79]; promotes cell migration[80]	Improved cell survival[79]; improved limb mobility and; improvement of growth promoting properties[81]	Improved cell; survival[79]
MSCs	Enhanced recovery of motor function, reduced damage of spinal neurons[82] Improved hindlimb function[83]	Improvement of motor function[84], structural and functional recovery of SCI[85,86] and axonal regeneration[86]	Improvement of proliferation, differentiation, immunomodulatory[87]; promoted the growth of blood vessels[88]; increase of expression of genes related to neural differentiated cells[89]

NSPCs: Neural stem/progenitor cells; OECs: Olfactory ensheathing cells; MSCs: Mesenchymal stem cells; BDNF: Brain-derived neurotrophic factor; NT-3: Neurotrophin-3; NGF: Nerve growth factor; SCI: Spinal cord injury.

[15]. The use of neurospheres containing NSPCs from olfactory mucosa is associated with difficulties in calculating the number of cells and the percentage of NSPCs in suspension.

Safety of cell-based treatments is a fundamental concern for regenerative medicine. Efficacy is usually the main focus, however, the safety of each treatment is also tested during the trials[16]. Clinical observations show that OEC transplantation is safe for patients and there were no serious adverse reactions in all cases[17]. Clinical trials of NSPCs and MSCs from the olfactory mucosa have not been performed to date.

NSPCs

NSPCs were discovered in the spinal cord and brain (in the subventricular area and the hippocampus), as well as the olfactory mucosa layer. These cells can differentiate into glial cells and mature neurons and encode neurotrophic factors for successful neuroregeneration[18-20].

The treatment of modelled spinal cord injuries includes suspension cell cultures in the form of neurospheres containing NSPCs. Studies have shown the effectiveness of neurospheres, from the olfactory mucosa, in the treatment of spinal cord injuries. Their transplantation in the acute phase of rat spinal cord injury contributes to the restoration of motor activity of the hind limbs and regeneration of axons of the rubrospinal tract[21,22].

Chronic injury of the spinal cord can be associated with pathological processes that lead to the formation of a posttraumatic cyst. The cyst can enlarge and compress the spinal cord, which complicates the processes of regeneration and mediation of nervous impulses to the limbs[23]. However, the application of these neurospheres in the chronic phase of spinal cord injury remains understudied. In the authors' laboratory, the first transplantation of neurospheres from the olfactory mucosa was performed in rats with modelled posttraumatic cysts. It was shown that transplantation contributed to the improvement of motor activity of the hind limbs and the reduction of the cyst size[24]. The proven effectiveness of neurospheres, obtained from olfactory mucosa in the experimental studies, can provide grounds for preclinical studies and further application in the treatment of spinal cord injuries in patients.

Ensheathing cells

OECs obtained from the olfactory mucosa are a unique type of glial cell found in the peripheral nervous system. In an adult organism, these cells manage the growth of new axons in the olfactory epithelium and protect a growing axon from growth-inhibiting factors, which allows an axon to grow to the size of an olfactory bulb and form a synapsis[25]. Besides, *in vitro* and *in vivo* studies have shown that OECs of an adult organism secreted molecules associated with myelinization: Protein zero (P0) and myelin basic protein[26]. It is suggested that this type of cells can maintain the growth and integrity of axons throughout an organism's life and contribute to the formation of the myelin sheath around demyelinated axons[27,28]. OECs can also express neurotrophic factors that promote neuroregeneration [29].

It has been shown that transplantation of OECs in the acute phase of spinal cord injury contributed to the regeneration of the nervous tissue and remyelination of axons, which leads to the restoration of limb motor activity. Furthermore, introducing these cells in the acute phase contributes to a reduction of posttraumatic astrogliosis[30]. Transplantation of OECs in the chronic phase promotes the recovery and growth of the damaged axons and improves limb motor activity[31]. In the authors' laboratory, for the first time, the therapeutic effect of OECs was shown in the treatment of posttraumatic spinal cord cysts. The transplantation of OECs contributed to a decrease in the volume of cysts and restoration of limb motor activity[32,33].

Preclinical studies have demonstrated the safety and efficacy of the use of olfactory mucosa cells in the treatment of acute and subacute stages of spinal cord injury[34-36]. The conducted clinical studies also demonstrated the safe use of autologous OECs in the treatment of patients with spinal cord injuries [37-39]. Thus, OECs from the olfactory mucosa can be considered the optimal cell material for personalised cell therapy in such patients.

MSCs

Experimental studies have shown that the transplantation of MSCs, derived from olfactory mucosa, contributed to the growth of axons in the injured rat nerves. A positive effect of these cells on the myelinization of axons was also evident *in vitro*[40]. However, MSCs derived from olfactory mucosa remain understudied in *in vivo* conditions.

MSCs obtained from bone marrow were also used in the treatment of spinal cord injuries. Even though the transplantation of these cells showed positive results in experimental models, clinical studies did not prove their effectiveness[41]. Besides, some studies describe the side effects of MSC transplantation, including neuropathic pain[15]. The application of MSCs obtained from olfactory mucosa can have the same consequences, which makes the other two types of olfactory mucosa cells (OECs and NSPCs) the most promising for cell therapy.

EXOGENOUS NEUROTROPHIN THERAPY

Another promising method for the treatment of spinal cord injuries is exogenous neurotrophin therapy since the endogenous neurotrophic factor count is insufficient for the regeneration of the injured tissue [42]. Neurotrophic factors, including nerve growth factor (NGF), neurotrophin-3 (NT-3), NT-4, and brain-derived neurotrophic factor (BDNF), play an important role in the processes of neuroregeneration and axon growth after injury[43].

One of the methods for delivering exogenous neurotrophins to the area of injury is injection. Studies conducted at the end of the last century have shown that the delivery of NGF for two weeks after resection of the spinal cord fragment in rats promoted the regeneration of the nervous tissue of the spinal cord[44]. Later, it was shown that the delivery of BDNF in the acute and chronic phases of rat spinal cord injury also contributed to nervous tissue regeneration[45,46]. Further *in vitro* studies showed that BDNF expressed by the OECs contributed to the transplant-mediated axon growth[47]. For the first time, the authors of this paper have demonstrated that the combined introduction of OECs and exogenous NT-3 to the modelled cysts in the rat spinal cord improved the motor activity of the hind limbs and reduced the cyst size[32]. The use of NT-3 improves the effects obtained from cell therapy and the data are presented in Figure 1[48].

However, after neurotrophins are directly administered to the area of injury, they degrade quickly. Currently, the most promising method of neurotrophin delivery to the area of injury is the use of adenoviral vectors[49]. There are direct and indirect deliveries of adenoviral vectors. Direct delivery involves the injection of the vector to the area of injury or nearby, resulting in the transduction of neurons, astrocytes, oligodendrocytes, macrophages, lymphocytes, and microglia. With indirect delivery, an adenoviral vector is injected intramuscular or into the peripheral nervous system.

Gene therapy *ex vivo* is a variant of indirect gene delivery. This therapy includes obtaining cells, genetic modification of these cells *in vitro*, and transplantation of a gene-cell construct into the patient [50]. Experimental studies investigated gene-cell constructs based on Schwann cells[51], MSCs[52,53], NSPCs[54,55], and OECs obtained from olfactory bulb[56]. In the authors' laboratory, an OEC-based gene-cell construct from the olfactory mucosa was studied. It was shown that transplantation of OECs obtained from olfactory mucosa, transduced by an adenoviral vector encoding a mature form of BDNF, into a post-traumatic cyst could have a therapeutic effect. This is observed not only due to increased secretion of neurotrophin but also due to the regenerative potential of the cells themselves[32]. Other authors showed the effectiveness of OECs obtained from olfactory mucosa transduced with adenoviral vector transcoding NT-3. This construct intensely encoded NT-3, which contributed to the growth of injured axons[57].

Thus, gene-cell constructs are being actively studied, however, it is necessary to continue the investigation of various combinations of cells and adenoviral vectors to create an optimal drug for gene-cell therapy. Special attention should be paid to the safety of this technology. Adenoviral vectors are the most studied in this respect. They are successfully used in the creation of vaccines and treatment of oncological diseases. At present, they are being actively studied for use in regenerative medicine. Although great success has been achieved in this field, it is necessary to improve the immune system response, the life span of the virus, and the packing ability of the vectors. However, the evolution of the adenoviral vector as a tool for the transfer of genetic material has revolutionized how doctors and scientists can approach the treatment of even the most debilitating diseases[58].

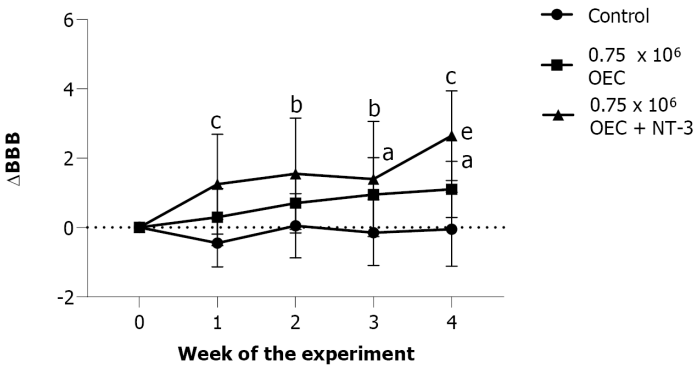

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Figure 1 Dynamics of recovery of hind limb motor activity in rats after transplantation of human olfactory ensheathing cell alone and in combination with neurotrophin-3 into SC cysts. $^{a}P < 0.05$, $^{b}P < 0.01$, $^{c}P < 0.001$ in comparison with the control; $^{e}P < 0.01$ in comparison with transplantation of olfactory ensheathing cell alone. Control = DMEM:F12 (1:1) without cells. Each group includes 10 animals. Neurotrophin-3 significantly improves the efficiency of olfactory ensheathing cells. OEC: Olfactory ensheathing cells; NT-3: Neurotrophin-3.

THREE-DIMENSIONAL BIOPRINTING IN THE TREATMENT OF SPINAL CORD INJURIES

Another promising method for delivering cells and neurotrophins to the area of injury is 3D bioprinting. The development of tissue-specific scaffolds that imitate the natural architecture of the studied tissue is the most important task of modern medicine. To create such structures, the field of 3D bioprinting is being actively explored. Scaffolds are printed layer-by-layer, using 3D printers, and each of the layers can be filled with cells and neurotrophic factors[9]. This technology has been actively studied for some years and has already been applied in the treatment of a wide range of pathologies, including spinal cord injuries[59].

The effect of 3D polymers on the restoration of nervous tissue is currently being studied in experimental models. For example, the transplantation of a printed 3D scaffold from biodegradable polyurethane, which contains mature neural stem cells (NSCs) of a mouse, positively affected the regeneration of the central nervous system of Danio-rerio embryos. Transplantation of this construct to adults with brain injury increased their survival rate and had a positive effect on the restoration of motor activity [60]. In addition, there are studies available on the application of printed agarose tubes in combination with mouse bone marrow stem cells after sciatic nerve injury in rats. It was shown that the application of this transplant was more effective in the restoration of motor and sensory activity than an injection of collagen or transplantation of nervous tissue into the area of injury. These studies showed that a solid scaffold increased cell survival rates and positively affected the regeneration of the damaged areas of nervous tissue[61]. The study of the application of a 3D printed polyethylene glycol gelatin methacrylate scaffold with rat neural progenitor cells (NPCs) also showed that transplantation of a scaffold with cells led to a better recovery of hind limbs motor activity in injured rats compared to groups that received cells without a scaffold or a scaffold without cells[62]. To improve the performance of 3D matrices, a combination of germanium phosphide and hyaluronic acid was developed. This construct significantly improved the recovery of motor activity of the hind limbs in rats with modelled spinal cord injury and also increased the migration of rat NPCs in the spinal cord to the area of injection [63].

A promising direction is the study of 3D printing based on OECs obtained from olfactory mucosa, since, as noted earlier, the production and application of these cells do not pose any danger to the patient. 3D microbeads were obtained from OECs and Matrigel. OECs survived the printing process and retained their phenotype. It is assumed that such a 3D construct can have a therapeutic effect when transplanted into the spinal cord of animals and promote the growth of axons along the scaffold[64].

Furthermore, there was a study made on the printed multichannel poly (propylene- fumarate)-collagen scaffold containing neurotrophin NT-3. Implantation of this construct into the spinal cord of an injured rat had a significant neurotrophic effect and contributed to the growth and regeneration of the damaged axons. The porous structure of the scaffold facilitated the migration of endogenous NSCs in rats and promoted neuronal regeneration[65].

However, materials used for 3D printing can rarely respond to the changes in the injured area or adapt to the changing shape, which is a limitation of such therapies. To remove these limitations, 4D bioprinting is being explored.

FOUR-DIMENSIONAL BIOPRINTING IN THE TREATMENT OF SPINAL CORD INJURIES

The development of more complex and "smart" materials will allow researchers to create novel polymers that have distinctive features: they change shape, can self-assemble, are capable of autonomous activation, and can capture a wide range of signals[66]. This type of polymer is used in 4D printing. Currently, these technologies are widely used in bone and skin grafting[67-70]. However, further research into the possibilities of 4D bioprinting will allow the use of four-dimensional polymers in the treatment of spinal cord injuries as well.

At the moment, a matrix has been developed that combines the developments of 3D printing with the advantages of novel technologies. Hybrid gelatin methacrylate-microcapsule hydrogel, in combination with polylactide-clicolide capsules with NT-3, can secrete growth factors at a certain level for 20 d. This, in turn, contributed to the recovery of the spinal cord after injury, differentiation of NSCs located in the spinal cord, and improvement in motor activity of the hind limbs in rats with spinal cord injury[71].

In parallel, a polymer based on epoxydated acrylate of soybean oil in combination with graphene and human MSCs was developed based on laser stereolithography technology[72]. In the present study, cells in the 4D polymer were placed in the medium for neural differentiation. Two weeks later, MSCs on the polymer showed a significantly higher level of neurogenic genes in comparison with the same cells cultivated on a regular 3D polymer. In addition, such material could reversibly change the structure and shape of memory[72]. These results allowed the authors to study MSCs on NSCs *in vitro*. A later study, by the same authors, focused on the design of polymer microwells with a memory function[73]. This was achieved by combining laser stereolithography, a polydimethylsiloxane mould, and organic glass for the formation of wells 400-800 μm in diameter. This approach allowed the authors to create a micro surrounding of a cell that could change its shape and achieve more favourable conditions for cell cultivation. NSCs in polymer showed a significant increase in the expression of markers of neural and glial differentiation compared to cultures cultivated on plastic and glass surfaces[73]. Another research group used technology based on polymer melt modelling and obtained an effect that was similar to that described above, from the cultivation of NSCs in combination with a polymer from polyurethane, nanoparticles, and gelatin. The resulting polymer also had a memory effect, was capable of maintaining its shape, and was suitable for cryo conservation[74].

PROSPECTS FOR THE APPLICATION OF OLFACTORY MUCOSA CELLS AND NEUROTROPHINS IN 4D BIOPRINTING

As already discussed in this review, olfactory mucosa cells have great potential in the treatment of spinal cord injuries and are optimal for personalised cell therapy. Four-dimensional bioprinting is a novel, actively developing direction in regenerative medicine. The application of olfactory mucosa cells and neurotrophins in the creation of 4D constructs will allow researchers to design unique transplants that will have a complex effect on damaged tissue. It is necessary to study 4D constructs based on both cells with the addition of a neutrophilic factor and transduced cells, which will intensively secrete various neurotrophic factors in the area of injury. Particular attention should be paid to constructs capable of adapting to changes in shape and size, which is especially important in the treatment of post-traumatic cysts.

CONCLUSION

The most promising vector for the development of spinal cord injury therapy is the development of smart 4D constructs. Such constructs can contain both neurotrophins and cells. The most optimal source of cells for 4D printing is olfactory mucosa due to its atraumatic production and proven therapeutic efficacy of the cells obtained from it. The study of 4D bioprinting based on olfactory mucosa cells and neurotrophic factors is necessary for developing an optimal strategy for the treatment of spinal cord injury.

FOOTNOTES

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MINIREVIEWS

Use of metaphors when treating unexplained medical symptoms

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Abstract

The words one chooses to describe personal pain mirror current usage, but may also hold echoes of an individual's lived experience. They may provide clues to the origin of physical symptoms that are medically hard to explain. The aim of this commentary is to propose, on the basis of the available literature, that verbal metaphors can prove effective in the psychotherapy of such conditions. I provide a case history of a 45 year old woman referred to psychiatry because of extreme 'burning' pain in her mouth and tongue. She had been to numerous doctors, had undergone a variety of tests, had tried many medical treatments, and had been prescribed a number of different pharmaceutical agents. She had changed her diet, done her daily dental mouth exercises, drunk a lot of water, but the burning continued and interfered, with her job (she was a teacher), her friendships, and her everyday life. This made her angry and recalcitrant to therapy, but the metaphor 'burning with rage,' as applicable to her pain, worked to establish a good alliance that led to a decrease of symptoms. Burning Mouth Syndrome is a medically unexplained condition of complex etiology that psychotherapy alone cannot reverse. The literature bears out, however, that the use of metaphors can help to open avenues of psychological exploration that accelerate adaptation to pain and improve quality life.

Key Words: Alexithymia; Burning mouth syndrome; Idioms of distress; Menopause; Metaphors; Pain

Core Tip: Burning mouth syndrome (BMS) is a medically unexplained pain condition of complex aetiology. It is particularly prevalent in menopausal and post-menopausal women. Like many complex disorders, BMS has many treatments, but none work well. The use of metaphor in psychotherapy may aid recovery by increasing patients' awareness of connections among mouth sensations, taboo emotions, and potential triggers in their personal and social environment.

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INTRODUCTION

Burning mouth syndrome (BMS), also known by many other names (glossodynia, orodynia, oral dysaesthesia, oral cenesthopathy, stomatodynia and stomatopyrosis) is characterized by pain in the mouth cavity, usually, but not always, concentrated on the tongue and roof of the mouth[1,2]. It affects women more than men, and generally begins in the menopausal years. Family physicians and dentists are the first to be consulted. When early attempts at treatment do not succeed, referrals are made to a number of different specialists, each with a partisan perspective on presumed cause and required intervention. The search for effective solutions is difficult because all blood tests results come back normal and no lesions are visible in the mouth. As a general rule, when there are many names for a syndrome, as is the case for BMS, the medical cause remains unexplained, and no one treatment works over the long term (Table 1).

The specialties involved with BMS include otolaryngology, neurology, gastroenterology, rheumatology, dermatology, psychology, and psychiatry[3]. A number of medications have been prescribed, as well as mouth washes, diets, and mouth exercises. Life style changes are often advocated, but most patients are not helped, probably because this condition result from many, perhaps interactive, causes that require close collaborative management.

BMS has been conceptualized as a consequence of aging tissues becoming vulnerable to infection, abrasion, and immune sensitization. Psychiatrists also consider psychological causation such as offense, grievance, slight, and indignity as precipitating factors. The immediate pathophysiology may include stress activation, and hormonal effects on salivary function[4,5], resulting in a dry and sensitive mouth [6] with accompanying disturbances in taste and loss of pleasure in eating[7,8]. Fear that the pain may be a sign of malignancy contributes to the chronicity of pain[9,10].

According to a recent meta-analysis of 18 studies[11], the prevalence of BMS (diagnosed only after all identifiable causes of orofacial pain had been excluded) ranges from 0.7% to 5.1% of the world population, 5.58% in Europe, 1.1% in North America, and 1.05% in Asia. The population age range of studies included in this meta-analysis was 40-85 years, with a case rate of 3.31% over age 50 and 1.92% under age 50. The gender ratio was 7:1 in favor of women[11]. One older study had found that the prevalence of BMS in a study sample recruited from a menopause clinic reached 26%[12]. Disorders such as BMS have been called 'mystery illnesses'[13], or syndromes of unexplained cause.

LITERATURE SEARCH

The idea for this paper originated in a chance meeting with a former patient whom I had last seen 25 years earlier. We met on the street and she made a point of stopping me and telling me that our meetings a quarter of a century ago had changed her life for the better. I was taken aback because I remembered our therapeutic sessions as difficult. She had presented with a diagnosis of BMS and her pain was still there when we terminated therapy. This led to a PubMed search for BMS AND Menopause AND Metaphor because the patient had been premenopausal at the time of our meetings and because I had used metaphors for 'burning' and for 'mouth' in an attempt to encourage her to talk about her life. I limited my search to papers published since 2000 except for references to the history of BMS itself and to the history of its psychological treatments. Because of the wealth of articles on various aspects of BMS, I leaned, for the most part, on general recent reviews. This is, therefore, a commentary. The opinions expressed are mine.

Table 1 Burning Mouth Syndrome

Symptoms	Visible signs	Etiology
Sore gums	None	Dental disease
Burning tongue	None	Infection; Allergy
Dry mouth	None	Dehydration
Altered taste	None	Gastric or dietary problems
Distress	Agitation; Social isolation	Psychiatric problems

CASE STUDY

A 45 year old teacher was referred to me for consultation on the initial assumption that her primary symptom, burning pain in her mouth and tongue, was a somatic delusion. On assessment, the patient was found to be self-aware, non-delusional, in considerable distress, and seeking psychotherapy for a pain that she thought must be psychologically-based since all potential immune and infective causes had been ruled out. Psychotherapy was made difficult, however, by the patient's anger directed at me because I represented the medical profession that had repeatedly failed to help with her distressing symptom. She had been frustrated at every turn in her search for answers to her pain. The patients had been given the diagnosis of Burning Mouth Syndrome, a form of somatic delusion, but I saw her as an angry woman. It was for this reason that I asked, during our first session, whether she was, perhaps, burning with rage. The patient did acknowledge being angry but did not see any connection between her anger and her pain. She did go on, however, to speak at length about the anger she felt at work. One of her colleagues had been promoted while she, who had worked at the school longer, had not. She then went on to tell me that this same colleague was currently away on a study sabbatical (which was a perk tied to her promotion) but was in actuality cheating on her husband, spending time with a lover behind her husband's back.

This conversation led, in subsequent sessions, to talking about the patient's own unpartnered and socially isolated state. I asked whether the "burnt out" metaphor applied to her, suggesting that, in comparison to her colleague's busy life, she might see her own life as lying "in ashes" *i.e.* dormant. This seemed to strike a chord. She talked about her lack of friends, her lack of family ties, and her current age making motherhood impossible. The motherhood theme turned out to be an important one. She was an only child and had always felt ill equipped to be a mother; she had had other ambitions. But now that motherhood was no longer a possibility, she deeply regretted many of her past decisions. In our sessions, she had become less angry and was talking more freely. Because she often mentioned male colleagues when talking about her work, I suggested that another common expression related to burning was "burning with lust." At this suggestion, she again became angry, saying that she didn't appreciate questions that were so personal. Shortly afterwards, she stopped therapy, claiming that her pain was better and she "didn't need me anymore." I always viewed this as a failed therapy until, 25 years later, we accidentally passed each other on the street. I did not recognize her. But she called out to me and stopped to talk. She said she was extremely grateful to me and that I had helped her immeasurably. She seemed sincere. Because our conversation was brief, I could not ascertain in what specific way she felt that our visits had been helpful. I did not think to ask permission to write about our therapy. Because of this, several potentially identifiable aspects of the case have been changed to protect the patient's identity.

RAGE AND MENOPAUSE

Hostility and anger were much in evidence in this patient. Ozcan *et al*[14], in a recent paper, discuss the prevalence of anger related to menopause and the significant losses (the loss of fertility, the loss of youth, vigor, health, the empty nest, the loss of opportunity, the death of parents) associated with this time of life. A previous psychotherapeutic case history of BMS[15] illustrates how addressing unexpressed rage led to a successful therapy outcome. There is little doubt in the literature that psychogenic components in general contribute to the interpretation of pain, and, thus, to its felt intensity. This probably starts in early life experiences that shape personality, pain tolerance, and cognitive styles, and that may lead to changes in somatic attributions and pain thresholds at later ages. Relevant to BMS in women, inflammatory markers increase at menopause[16,17]. This provides a model by which stress determinants can act over extended periods of time and eventually trigger symptoms at a time of hormonal change.

Anxiety and depression and BMS

Onset of BMS symptoms is often reported as occurring in the context of depression or anxiety disorder. Kim *et al*[18] conducted a population-based study using the Korean National Health Insurance Service National Sample Cohort database. Their aim was to determine the prevalence of psychopathology in patients with a clinical diagnosis of BMS and compare it with that of a matched group from the general population. What they found was an excessive rate of anxiety and depression associated with BMS. Because patients with a history of psychopathology prior to BMS had been excluded from this study, their conclusion was that anxiety and depression did not cause BMS but, rather, resulted from BMS. Their findings, however, could indicate that a vulnerability to anxiety and depression, previously unexpressed, had been triggered by the distress associated with the symptoms of BMS[19] or by hormonal changes not addressed in the study.

PERSONALITY FEATURES AND BMS

Another avenue of psychological investigation in BMS has been personality. Specific personality traits have been associated with BMS[20,21], two of which stand out: (1) A discomfort with novel experiences; and (2) a tendency to use avoidance as a mechanism of defense against anxiety. Researchers pursuing this route of investigation are persuaded that personality features are as important to the course and outcome of BMS as are the physiological processes (neurogenic, immune, endocrine) usually highlighted in the BMS literature.

Physical distress, especially the experience of pain, may theoretically result from a deficit in the cognitive processing of emotions and the inability to express one's feelings in words, such that the emotion is, instead, expressed somatically[22]. This can be a feature of personality and is referred to as alexithymia. It is usually assessed by scores on the 20-item Toronto Alexithymia Scale (TAS-20)[23,24]. High alexithymia scores are associated with chronic pain, negative affect, and low perceived quality of life[25]. Alexithymia scores have been reported as significantly higher in BMS patients than in matched controls recruited from the general population[26,27].

WORDS USED TO EXPRESS PAIN

In an attempt to treat each pain patient not as a case but as an individual[28], and to find the most appropriate and effective treatment for each, researchers have taken an interest in the specific words that patients use to describe their personal pain. Melzack and Torgerson[29] and Melzack[30] systematically compiled a list of adjectives that describe pain states and used them to construct the currently most widely utilized pain screen, the McGill Pain Questionnaire.

Kirmayer *et al*[31] proposed that somatic symptoms often represent, through the symbolism of word associations and metaphors available within a specific culture, culture-specific idioms of distress. This possibility links the specificity of words used to describe physical distress with the psychological and social history and circumstances of individual patients. An earlier paper[32] had suggested that the sensation, expression and etiology of a set of symptoms are all components of a semantic network, with every pain-evoking condition eliciting descriptive words from that network. The network is formed by connections established over a life time between somatic sites of pain and emotionally meaningful relationships or between pain and perceived decline in social status.

HISTORY OF CONCEPTUALIZATIONS OF BMS

The developmental history of concepts relating to BMS is pertinent here[33]. Although first descriptions of a syndrome of mouth pain begin to emerge in the European medical literature at the beginning of the 19th century, it is not until 1870[34] that the pain is characterized as "burning". In North America, it is not until 1920 that there is a first reference to a "burning tongue"[35]. In that paper, the distress caused by a burning tongue was attributed to a fear or phobia of tongue cancer[35]. The first references to the current favourite, "burning mouth syndrome," start appearing in the English language dental literature in 1967[36,37]. Since then, over a thousand entries are listed under BMS in Google Scholar.

References to 'Burning' in English

Although common expressions and metaphors for pain differ in different languages and cultures[38-40], the concept of burning pain brings with it its own specific imagery in English. One image is of the flame of erotic passion as in "Burnin for you," a rock band song that was a #1 hit song in the United States in the early 1980s. The same idea is captured in informal American speech, *-e.g.* "having the hots for someone." Because BMS is associated with postmenopausal women, psychotherapists may not expect metaphors of lust to be pertinent to this age group. Sexual desire is widely considered to abate at

this time in a woman's life[41]. However, for many women after menopause, freed from the fear of unwanted pregnancy, interest in sexual activity increases, often directed outside of legitimate channels [42-44]. Older age does not eliminate lust, as well expressed by one resident in an assisted living facility when asked how she felt about this topic: "Snow on the mountain, fire in the furnace—just because I'm old don't mean the other parts of me aren't hot"[45].

BURNOUT AND MENOPAUSE

The concept of "burnout," indicating a state of exhaustion, mental fog, loss of *joie de vivre* caused by excessive and prolonged work stress[46], has been associated with menopause[47,48]. Of all the symptoms experienced by women when they reach menopause, fatigue is one of the most common and is reportedly the one most subjectively distressing[48]. Physical pain may be part of the picture[49]. The burnt out feeling, the belief that there's no further joy to expect in life, nothing to look forward to, constitutes a major emotional burden. In an article about women with functional voice disorder or dysphonia, Baker *et al*[50] comment that the women had not only lost the use of their voice, literally, but were feeling burnt out because their figurative 'voice' was not being heard.

MOUTH AND FLAMES

Mouths and tongues lend themselves to metaphors because they serve a multitude of functions. They are used not only to speak but also to eat, to make love, to whisper, to challenge, to sing, to yawn, to wail, and to yell, which leads to many possible connections to malaise and distress[51]. Biblical proverb 16:27, links mouths with flames - "A worthless man plots evil, and his speech is like a scorching fire[52]" Since the time of Homer, teeth and tongue and lips have been symbolically viewed as fences or barriers that prevent rash thoughts from being voiced. They form a virtual barricade against airborne poisons, not only infective agents and poisonous gases, but also toxins such as insults, humiliations, and slanders)[53].

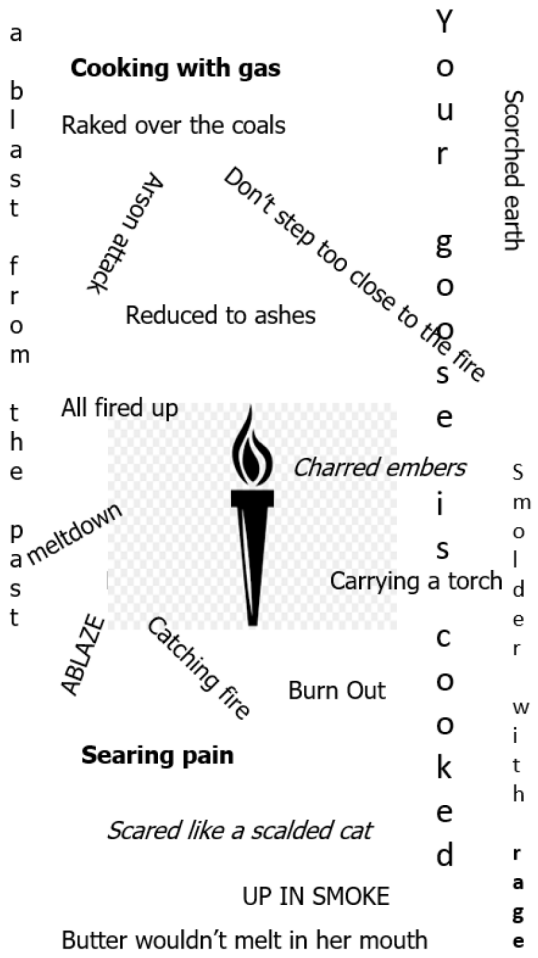
Idiomatic speech in English links the tongue to the infliction of pain (*e.g.* 'tongue lashing,' 'chewing out,' 'giving someone the rough side of one's tongue')[54]. Disgust and deceit are further negative oral associations ("leave a bad taste in the mouth," "forked tongue," "doing lip service to")[55]. This may help to explain how the mouth becomes a fertile site for psychosomatic pain.

Please see Figure 1 for fire and heat metaphors that could psychologically underpin BMS symptoms.

PATIENT-THERAPIST COMMUNICATION

Assuming an association among experience, symbolization, and somatic symptoms can lead to symptom improvement, perhaps through new confidence that symptoms have personal meaning and the unknown is less to be feared. Confidence in understanding the multidetermined sources of a symptom depends to a large extent on the communication between patient and therapist. Current recommendations re therapy with BMS patients are: total transparency with BMS patients, admission that the condition is poorly understood, acknowledgement that both cause and optimal treatment are uncertain, but also explanation that psychological factors play a role. The patient should not be led to expect immediate cure[56]. While symptom amelioration is hoped for, the goal of therapy is a deepening of the understanding of the mind-body connection.

What is generally agreed as fundamental to effective therapy of BMS is that the clinician listen carefully to what the patient says[57]. The introduction of metaphors into the conversation has been found useful for starting therapeutic dialogues and opening channels of communication that can lead to healing. Gallagher *et al*[58] conducted a randomized-controlled trial investigating the impact of metaphors on the reconceptualization of pain. They found that pain biology was better understood when study participants were given a booklet of metaphors to read (73%) in comparison to participants who, instead, were given an educational booklet on cognitive-behavioral principles (43%). Reading about metaphors also decreased pain catastrophizing in this study, but there was no positive impact on pain or disability. A more recent study found that a mutual appreciation of pain metaphors enhances communication between pain patients and their doctors[59]. Metaphors engage patients in discussion about psychological discomforts, which then leads naturally to conversation about relationships, hopes, disappointments, and regrets. With time, patients share stories of the stresses in their lives. According to Sapolsky[60], real (literal) and symbolic (metaphorical) versions of a concept are processed in the same exact brain regions. When doctors use metaphors, it allows patients to reframe their distress in new ways[61]. Clinicians can be the ones who introduce new metaphors, but commentators agree that the most fruitful metaphors are those generated by the patients themselves[62]. Shinebourne and Smith[63] suggest that patient-generated metaphors offer a 'safe bridge' through which patients express emotions



DOI: 10.12998/wjcc.v11.i2.332

Figure 1 Burning mouth.

that are too hard to put into straightforward words.

Adjectives, such as 'burning' that patients use to describe their pain, allow therapists to elaborate richly-linked metaphors. The therapist can suggest, for instance, that feeling wronged by disloyal husbands, unappreciative employers, successful rivals, or feeling mad at oneself for wrong turns taken, or simply feeling hurt by the general unfairness of life, can make one 'burn with rage.' Recognizing and expressing anger safely has long been considered helpful for sufferers of chronic pain[64]. Increasing awareness of connections between the sensations in one's mouth, one's taboo emotions, and the stresses and potential triggering factors in one's personal and wider environment is a start on the path that leads to accommodating oneself to pain[18,65,66]. Symptoms are unlikely to be fully eliminated, but they become easier to set to the side.

DISCUSSION

Various interventions to alleviate symptoms and improve quality of life in BMS are continuously being tried. This includes pharmacological treatment, transmagnetic stimulation, cognitive behavioral and psychoanalytically-informed psychotherapy[67,68], but rarely has any one treatment reliably resulted in remission. Reportedly only 3% of patients lose their symptoms altogether[69,70].

This review recommends psychotherapy that builds on the words with which BMS patients describe their pain. This allows collaborative exploration, with the patient, of all the potential symbolic meanings of the words that best express the nature of the pain. Burning has many connotations, but some patients may use adjectives other than burning to describe oral pain. They may use words such as 'tingling' (suggesting excitement) or 'dryness' (suggesting lovelessness) or 'numbness' (suggesting repeated hurt). Many patients who suffer from BMS have been described as alexithymic, in other words, as having chronic difficulty recognizing or talking about emotions. Because of this, images instead of words have been used to good effect[71]. Introducing metaphors constitutes another potentially useful avenue that can result in meaningful communication[72].

Table 2 Putting metaphors to use

Patient descriptions of unexplained oral pain	Potential English metaphor
Burning	It burns me up: Makes me extremely angry
Gripping	To lose one's grip: To lose control over one's world
Throbbing	Heart throb: Someone you find extremely attractive
Crawling	Crawl out of the woodwork: The emergence of something unpleasant
Sore	To get sore at: To get angry with
Raw	To get a raw deal: To be taken advantage of
Shooting	To be gun-shy: To be wary, apprehensive because of past bad experience

The challenge for those treating or witnessing pain is to find a way of crossing the chasm of meaning between themselves and the person living with pain[73] (Table 2).

CONCLUSION

This paper suggests that the symptoms of burning mouth syndrome hold particular significance for menopausal women and that the use of metaphor in psychotherapy may aid recovery by increasing patients' awareness of connections among mouth sensations, taboo emotions, and potential triggers (or sustaining factors) in their personal and social environment.

FOOTNOTES

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ORIGINAL ARTICLE

Case Control Study

Microvesicles with mitochondrial content are increased in patients with sepsis and associated with inflammatory responses

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Abstract

BACKGROUND

Endothelial activation plays an important role in sepsis-mediated inflammation, but the triggering factors have not been fully elucidated. Microvesicles carrying mitochondrial content (mitoMVs) have been implicated in several diseases and shown to induce endothelial activation.

AIM

To explore whether mitoMVs constitute a subset of MVs isolated from plasma of patients with sepsis and contribute to endothelial activation.

METHODS

MVs were isolated from human plasma and characterized by confocal microscopy and flow cytometry. Proinflammatory cytokines, including interleukin (IL)-6, IL-8 and tumour necrosis factor (TNF)-α, and soluble vascular cell adhesion molecule (sVCAM)-1 were detected by ELISA. Human umbilical vein endothelial cells (HUVECs) were stimulated with the circulating MVs to evaluate their effect on endothelial activation.

RESULTS

MitoMVs were observed in plasma from patients with sepsis. Compared with those in healthy controls, expression of MVs, mitoMVs, proinflammatory

cytokines and sVCAM-1 was increased. The number of mitoMVs was positively associated with TNF-α and sVCAM-1. *In vitro*, compared with MVs isolated from the plasma of healthy controls, MVs isolated from the plasma of patients with sepsis induced expression of *OAS2*, *RSAD2*, and *CXCL10* in HUVECs. MitoMVs were taken up by HUVECs, and sonication of MVs significantly reduced the uptake of mitoMVs by HUVECs and expression of the above three type I IFN-dependent genes.

CONCLUSION

MitoMVs are increased in the plasma of patients with sepsis, which induces elevated expression of type I IFN-dependent genes. This suggests that circulating mitoMVs activate the type I IFN signalling pathway in endothelial cells and lead to endothelial activation.

Key Words: Sepsis; Microvesicles; Mitochondria; Microvesicles carrying mitochondrial content

Core Tip: Sepsis is a systemic inflammatory response syndrome that can lead to multiple organ dysfunction related to endothelial injury. Increased numbers of circulating microvesicles carrying mitochondrial content (mitoMVs) have been found in patients with systemic lupus erythematosus, which feature inflammation as the pathogenic mechanism. Mitochondrial damage-associated molecular patterns have been shown to induce endothelial activation. Therefore, the presence and function of mitoMVs in sepsis was studied. We found that mitoMVs were increased in plasma of patients with sepsis, and were related to inflammatory markers and induced elevated expression of type-I-IFN-dependent genes in endothelial cells.

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INTRODUCTION

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated systemic inflammatory response to infection[1], and is characterized by high mortality and substantial morbidity rates[2]. In this dysregulated systemic inflammatory response, endothelial cells (ECs) are increasingly believed to play a crucial role[3]. By shifting to a proinflammatory and pro-adhesive phenotype, activated ECs can amplify the inflammatory response. Moreover, due to the reduced production of NO, activated ECs can impair microcirculatory blood flow, leading to organ injury and even life-threatening organ failure. Therefore, better characterization of the molecular mechanisms of endothelial activation may have diagnostic and therapeutic value for this potentially fatal disease.

Microvesicles (MVs), also called microparticles, are extracellular vesicles that expose phosphatidylserine (PS). They range in diameter from 0.1 to 1 μm and can be released under both physiological and pathological conditions[4]. Thus, in addition to healthy conditions, MVs can be released under disease conditions, especially diseases that are accompanied by EC activation, such as coronary heart disease[5], type 2 diabetes[6], sepsis[7], and systemic lupus erythematosus[8]. Compared with control groups, the number of MVs in patients with the above diseases tended to increase significantly. More interestingly, by transferring nucleic acids, receptors, organelles, proteins and lipids to target cells[9], MVs can also affect the biological functions of recipient cells. In terms of endothelial activation, MVs released from lipopolysaccharide (LPS)-stimulated monocytes can induce the expression of a variety of adhesion molecules in ECs[10], and MVs isolated from the plasma of patients with sepsis can even mediate vascular function[11]. Therefore, MVs are proposed to mediate endothelial activation in sepsis.

MVs carrying mitochondrial content (mitoMVs) have been reported in LPS-stimulated monocytes [12]. In addition, increased numbers of circulating mitoMVs have been found in patients with systemic lupus erythematosus[8] and in mouse models of hepatic inflammation[13]. In particular, extracellular mitochondria and mitochondrial damage-associated molecular patterns (DAMPs) are identified as inducers of endothelial activation. On the other hand, sepsis changes the activity of mitochondria, which are essential intracellular regulators of the immune response[14,15]. Therefore, we aimed to test the hypothesis that mitoMVs constitute a subset of MVs isolated from the plasma of patients with sepsis and contribute to endothelial activation.

MATERIALS AND METHODS

Study design and patient population

This study was approved by the Ethics Committee of the First Affiliated Hospital of University of South China. Patients who received medical intensive care for the treatment of sepsis from 2019 to 2020 were recruited. Informed consent was obtained before initiating the study. Adult patients (age 18–85 years) diagnosed with sepsis were recruited. The diagnosis relied on "The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)"[1]. The control group was composed of healthy volunteers who visited the physical examination centre of our hospital during the same period. Patients who were younger than 18 years or older than 85 years, took corticosteroids or immunosuppressive medications prior to arrival, or did not sign the informed consent form were excluded. Information on all subjects enrolled in the study, including their age, sex, medical history, white blood cell count, and some blood parameters, was collected and recorded at the first visit.

Blood collection and preparation

Peripheral venous blood samples were drawn and preserved according to previously published protocols. First, after the subjects had fasted for 8 h, whole blood was collected intravenously, but the first tube of blood was discarded. Serum blood tubes and 3.2% trisodium citrate anticoagulant tubes were used to collect the samples, which were placed in an upright position to prevent shaking. These samples were centrifuged at 2000 *g* for 10 min to prepare serum and platelet-rich plasma. Platelet-rich plasma was then centrifuged again at 2000 *g* for 10 min to prepare platelet-poor plasma (PPP). PPP and serum samples were stored at -80°C for later use.

Isolation and probing of MVs

Flow cytometry was used to identify and count the MVs of different surface molecules. PPP (250 μL) was mixed with 300 μL of PBS and centrifuged at 2000 *g* for 10 min at 20°C to remove apoptotic bodies and debris. The upper 500 μL of plasma was transferred to a new tube and centrifuged at room temperature for 30 min at 18000 *g* to concentrate the plasma MVs. The top 450 μL of plasma was removed, 500 μL PBS was added, and the MVs were recentrifuged. Finally, 400 μL of supernatant was removed, and the remaining 150 μL of MVs was divided into two parts. Fifty microlitres of the remaining MVs was transferred into a flow cytometry tube for the following experiments. The other 100 μL of MVs was stored at -80°C. For *in vitro* experiments, 2 mL PPP was centrifuged according to the above protocol; however, after the last centrifugation, almost all of the supernatant was discarded, and only 100 μL of the MV pellet was retained and stored at -80°C for later use.

For flow cytometry, to identify the total MV population and determine whether it contained mitochondrial content, a 50 μL MV suspension was incubated with the following fluorescent monoclonal antibodies: APC-labelled anti-tom22 (translocase of the outer mitochondrial membrane 22) (Cat. No. 130-107-698; Miltenyi Biotec, Germany) and FITC-labelled lactadherin (lot no. HH0430-1ML; Haematologic Technologies, United States). In addition, MitoTracker Deep Red (Cat. No. M22426; Invitrogen, Carlsbad, CA, United States) was used to assess the mitochondrial content. After incubation at room temperature for 15 min, FITC- and APC-conjugated isotype control antibodies were used as controls. Calibration beads (Cat. No. F13839; Thermo Fisher Scientific, United States) were used as a size reference. Finally, MVs were identified and counted using a BD Aria II flow cytometer (BD, United States). MV analysis was performed at the second gear flow rate, and light scattering and fluorescence were determined using a logarithmic model. Events that were 0.1-1.0 μm in diameter on FSC-SSC plots and emitted green fluorescence were defined as MVs. FlowJo (Version 7.6.1; BD) was used to obtain and analyse the data. The number of MVs per microlitre of plasma was calculated as previously described [16].

For confocal microscopy, MVs were labelled with MitoTracker Deep Red for 15 min and with lactadherin-FITC for 15 min, followed by washing and mounting on glass slides coated with 50% glycerin. The slides were observed under an LSM 880 confocal microscope (Carl Zeiss, Jena, Germany) in the Medical Instrument and Equipment Technology Laboratory of Hengyang medical college, University of South China.

ELISA

ELISA was used to detect the serum expression levels of tumour necrosis factor (TNF)-α, interleukin (IL)-6, IL-8, C-reactive protein (CRP) and soluble vascular cell adhesion molecule (sVCAM)-1 (Thermo Fisher Scientific). ELISA plates were coated with the capture antibody at 100 μL/well and incubated overnight at 4°C. The next morning, serum samples were thawed and centrifuged at 1000 *g* for 15 min before use. Then, 100 μL of the diluted sample was added to the appropriate ELISA plate. The ELISA plate was again incubated overnight at 4°C for maximum sensitivity. On the third morning, 100 μL of the diluted detection antibody was added to each well, followed by incubation at room temperature for 1 h. Subsequently, 100 μL of diluted streptavidin–horseradish peroxidase was added to each well and incubated at room temperature for 30 min. Then, 1´ tetramethylbenzidine substrate solution was added at 100 μL/well and incubated at room temperature for 15 min. Finally, 100 μL of Stop Solution was

added to each well, and absorbance was read at 450 nm.

Cell culture, stimulation and MV sonication

Human umbilical vein endothelial cells (HUVECs) were maintained in endothelial cell medium (ECM, ScienCell, USA), comprising basal medium, 5% foetal bovine serum, 1% endothelial cell growth supplement, and 1% penicillin/streptomycin solution, at 37°C in a humidified 95%:5% (v/v) mixture of air and CO_2. When HUVECs reached approximately 80% confluence, they were digested and seeded in a 12-well plate (Nest, Wuxi, China). Before treatment with MVs, the ECM was replaced with FBS-free culture medium, and the MVs were quantified by flow cytometry. The cells were treated with equal numbers of MVs from the plasma of healthy controls (MVcontrol) and MVs from the plasma of patients with sepsis (MVsepsis) for 8 h. Cell-free supernatants were collected for the measurement of IL-8 by ELISA. Total RNA was extracted from the cells, and quantitative reverse transcription polymerase chain reaction (qRT-PCR) was used to determine expression of *IL-8, CXCR2, RSAD2* and *OAS2*. The primers for these genes are shown in Table 1.

MVs were resuspended and diluted in ECM to the desired concentrations. Sonication of the samples was performed using an ultrasonic processor (VCX130, United States) at 100% power and 6´ 30-s sonication rounds at 1-min intervals.

qRT-PCR

RNA was isolated from cells by using TRIzol™ Reagent (Cat. No. 15596026; Thermo Fisher Scientific), and cDNA synthesis was performed using a RevertAid First Strand cDNA Synthesis Kit (Cat. No. K1622; Thermo Fisher Scientific). The CFX96 system (Bio-Rad Laboratories) and TB Green® Premix Ex Taq™ II (Cat. No. RR820A; Takara, Tokyo, Japan) were used for real-time PCR-based quantifications. The expression levels of the mRNAs of interest were determined using the delta Ct method and normalized to the GAPDH mRNA level.

MitoTracker-positive MV uptake was measured by flow cytometry and confocal microscopy

For flow cytometry, HUVECs were seeded in 12-well plates on 12-mm coverslips (Cat. No. 1254580; Fisher). MVs isolated from patients with sepsis were labelled with MitoTracker Deep Red and centrifuged at room temperature for 30 min at 18000 x *g*. The MVs were washed with PBS and recentrifuged. Before incubation of HUVECs with MVs, the cell culture medium was replaced with fresh FBS-free medium, and the cells were starved for 2 h. MVs were suspended in the same FBS-free medium supplemented with 200 g/mL bovine serum albumin and added to the HUVECs for 2 h at 37°C. Afterwards, the cell supernatant was discarded, and the HUVECs were washed with warm PBS. Subsequently, the coverslips were placed in a single-well Petri dish and processed separately, and the remaining HUVECs in the 12-well plates were detached by trypsinization and fixed with 2% paraformaldehyde (PFA) for flow cytometry.

For immunofluorescence confocal microscopy, HUVECs growing on coverslips were directly fixed with 4% PFA in PBS (pH 7.4) for 15 min at 37°C, quenched with 150 mmol/L Tris pH 8.0 for 5 min, and washed three times with PBS. Nuclei were stained with Hoechst (10 mmol/L in PBS) for 3 min. Coverslips were mounted on concave microscope slides coated with PBS and sealed, and images were acquired on a Zeiss LSM 880 confocal microscope. MitoTracker-labelled MVs were excited with a 543 nm laser and nuclei were excited with a 405 nm laser.

Quantification and statistical analysis

SPSS version 26.0 was used for statistical analysis. Before statistical analyses, data were tested for normal distribution by the Shapiro–Wilk test. Data that fitted the assumption of normal distribution were presented as the mean ± SEM, and Student's *t* test was used to compare data from two groups. Non-normally distributed data were presented as the median (first to third interquartile range) and analysed by the Kruskal–Wallis test. Categorical data were analysed by the χ^2 test, followed by *post hoc* Wilcoxon signed-rank test. If the prediction frequency was < 5, Fisher's exact test was used. Correlations between MVs and cytokines were evaluated with scatter plots and Spearman rank correlation coefficients. $P < 0.05$ was considered significant. $^aP < 0.05$, $^bP < 0.01$.

RESULTS

Baseline characteristics of the study population

The demographic parameters of the patients with sepsis and healthy controls are shown in Table 2. During the study period, on the basis of the inclusion and exclusion criteria, 19 patients with sepsis and 20 control volunteers were finally included. No differences in age, sex, or history of hypertension or diabetes mellitus were observed between the two groups. However, the white blood cell count was significantly higher in the sepsis group ($P < 0.001$). Microbiological tests were carried out for all patients with sepsis, revealing 13 (68.4%) Gram-negative bacterial infections and 3 (15.8%) Gram-positive

Table 1 Primers were used in this study for quantitative reverse transcription polymerase chain reaction

Gene	Forward primer	Reverse primer
IL-8	CTCTTGGCAGCCTTCCTGATT	TATGCACTGACATCTAAGTTCTTTAGCA
OAS2	ACGTGACATCCTCGATAAAACTG	GAACCCATCAAGGGACTTCTG
RSAD2	TGAGGTTCTGCAAAGTAGAGTT	GCGAGAATGTCCAAATACTCAC
CXCL10	GTGGCATTCAAGGAGTACCTC	TGATGGCCTTCGATTCTGGATT

Table 2 Patient Characteristics and plasma cytokine concentrations

	Control (*n* = 20)	Sepsis (*n* = 19)	*Psepsis vs control*
Characteristics			
Age[a]	62.5 ± 9.8	58.13 ± 9.69	0.346
Male sex[c]	11	7	0.256
Hypertension[c]	4	6	0.480
DM[c]	1	2	0.605
WBC, 10^9/L[b]	6.18 ± 1.57	14.19 ± 8.02	< 0.001
Site of infection			
Pneumonia	NA	6	
Urinary	NA	6	
Abdominal	NA	5	
Bacteraemia	NA	2	
Unknown	NA	3	
Microbial data			
Gram positive	NA	3	
Gram negative	NA	13	
Fungi	NA	1	
Mixed	NA	2	
Unknown	NA	4	
Inflammation markers			
TNF-α (pg/mL)[b]	6.90 (4.94-9.45)	26.10 (17.56-35.02)	< 0.001
IL-6 (pg/mL)[b]	7.33 (4.68-10.33)	61.25 (37.54-87.30)	< 0.001
IL-8 (pg/mL)[b]	7.30 (5.11–9.00)	19.59 (14.04-62.19)	< 0.001
CRP (ng/mL)[b]	158.62 (67.75-246.42)	445.07 (382.31-549.73)	< 0.001
sVCAM-1 (ng/mL)[b]	89.22 (72.09-99.67)	164.68 (134.15-198.55)	< 0.001

[a]Mean ± SD determined by *t*-test.
[b]Median (interquartile range) tested by the Kruskal-Wallis test.
[c]The rate or constituent ratio between the two groups was analyzed by the chi-square test.
IL-6: Interleukin-6; IL-8: Interleukin-8; TNF-α: Tumour necrosis factor-α; CRP: C-reactive protein; sVCAM-1: Soluble vascular cell adhesion molecule-1; NA: Not available.

infections. In terms of the source of infection, the most common sites of original infection in the sepsis group were the lungs and urine, followed by the abdomen and bloodstream.

MVs released by patients with sepsis are increased in mitochondrial content

Because MVs are membrane vesicles with diameters ranging from 0.1 to 1 μm, 0.2 μm, 0.5 μm and 1 μm particle standards were used to optimize the flow cytometer before circulating MVs were analysed by flow cytometry. The Aria II flow cytometer with a logical display was capable of distinguishing the

above standards (Figure 1A). Most of the MVs separated from plasma were within our delineated range (Figure 1B), and the number of the circulating MV peaks appeared between 0.2 and 0.5 μm (Figure 1C). This result was similar to a previous report[17], indicating that our centrifugation and detection protocol was feasible.

Confocal scanning microscopy and flow cytometry were used to examine whether the MVs isolated from the plasma of patients with sepsis were rich in mitochondrial content. The binding of lactadherin to PS was used to distinguish MVs from events caused by noise or exosomes. MitoTracker Deep Red and APC-anti-tom22 were used to indicate whether the MVs contained mitochondrial components.

Bright field microscopy revealed that the MVs were approximately elliptical in shape and of different sizes (Supplementary Figure 1). Upon laser excitation at wavelengths suitable for FITC and MitoTracker Deep Red, some of the MVs appearing in the bright field image were excited to emit green and red fluorescence, respectively. Some of the MVs appeared yellow when the bright field and fluorescent images were merged (Supplementary Figure 1). This result suggests that the extracellular vesicles isolated from the plasma of patients with sepsis are indeed MVs and carry mitochondrial components.

To correctly identify mitoMVs, we determined a flow cytometry threshold with a blank MV sample to correct for intrinsic autofluorescence (Figure 2A). To correct for spectral overlap, we also incubated the MV samples with lactadherin-FITC, anti-tom22-APC or MitoTracker Deep Red to establish thresholds. These thresholds are shown in Figure 2B, C and E. The MVs from septic patients stained positive for both lactadherin and tom22 (Figure 2D) and for both lactadherin and MitoTracker (Figure 2F), confirming the presence of mitochondrial components.

Expression of MVs, mitoMVs, sVCAM-1 and inflammatory markers in the sepsis and control groups

We determined the numbers of MVs and mitoMVs in plasma samples from the patients with sepsis and controls. The number of MVs in the healthy controls was 23.72 (20.10–30.21) × 10^6 events/μL, whereas that in the sepsis group was 73.27 (64.08–84.49) × 10^6 events/μL. These numbers were significantly different between the two groups ($P < 0.001$; Figure 3A and B). We analysed the number of mitoMVs in the healthy control and sepsis groups. The number of mitoMVs in the healthy control group was 3.12 (2.16–3.82) × 10^6 events/μL, and that in the sepsis group was 22.53 (17.78–32.29) × 10^6 events/μL. These values also suggested significant differences between the two groups ($P < 0.001$; Figure 3C and D, respectively). Regarding cytokines, the plasma levels of the endothelial activation marker sVCAM-1 and the inflammatory markers IL-8, IL-6, TNF-α and CRP were dramatically increased in patients with sepsis after their admittance to intensive care units and diagnosis compared with the healthy control group, and the difference was significant ($P < 0.001$; Table 1). These data suggest that, in the plasma of patients with sepsis, the increase in the number of mitoMVs was more significant than the increase in the number of MVs and there were endothelial dysfunction and severe inflammatory response in patients with sepsis.

Association among TNF-a, sVCAM-1 and MVsepsis and induction of IL-8 in HUVECs

Because MVs and mitochondrial components are related to endothelial dysfunction[18] and inflammation[19], we analysed the relationships among MVs, mitoMVs and cytokines in sepsis. In the sepsis group, the number of mitoMVs was related to expression of TNF-α ($P = 0.022$, $r = 0.521$; Figure 4B, respectively) and to expression of sVCAM-1 ($P = 0.041$, $r = 0.472$; Figure 4C, respectively). Second, expression of MVs was related to expression of TNF-α ($P = 0.027$, $r = 0.507$; Figure 4A), but the correlation coefficient was lower than that of mitoMVs and TNF-α. Finally, we did not find IL-6, IL-8 or CRP to be correlated with MVs or mitoMVs despite performing the same correlation analysis.

Since TNF-α is a strong proinflammatory factor and sVCAM-1 is a marker of endothelial activation, the above results indicate that MVsepsis may mediate the sepsis-induced inflammatory response through the endothelium. Therefore, we isolated MVs from the plasma of patients with sepsis and healthy controls and applied them to HUVECs *in vitro*. Compared with MVcontrol, MVsepsis induced an increase in IL-8 mRNA expression in HUVECs. In the HUVEC supernatant, IL-8 expression in the MVsepsis treatment group was significantly higher than that in the MVcontrol treatment group ($P < 0.05$, Figure 4D). This indicates that MVsepsis are able to activate ECs.

MitoMVs are internalized by HUVECs and can induce activation of type I IFN response in HUVECs

Given that MVs exert their biological effects by transferring their cargo to recipient cells[20,21], confocal microscopy was used to explore whether the mitochondrial content in MVsepsis could be taken up by HUVECs. Incubation of MVsepsis with HUVECs resulted in accumulation of MitoTracker-positive MVs around the nucleus and in the significantly increased red fluorescence intensity of HUVECs, which indicated that mitochondrial content of MVsepsis was transferred to HUVECs (Figure 5).

Since several components of mitochondrial DAMPs have the capacity to induce activation of type I IFN response[22], we determined the mRNA expression levels of *CXCL10*, *RSAD2* and *OAS2*, all of which are representative of the type I IFN signalling pathway, in HUVECs stimulated by circulating MVs. qRT-PCR showed that, compared with MVcontrol, MVsepsis significantly promoted HUVEC expression of the above genes ($P < 0.01$, Figure 6). Among these genes, *CXCL10* expression was increased to the greatest extent (approximately 500-fold). In addition, the treatment of MVsepsis by

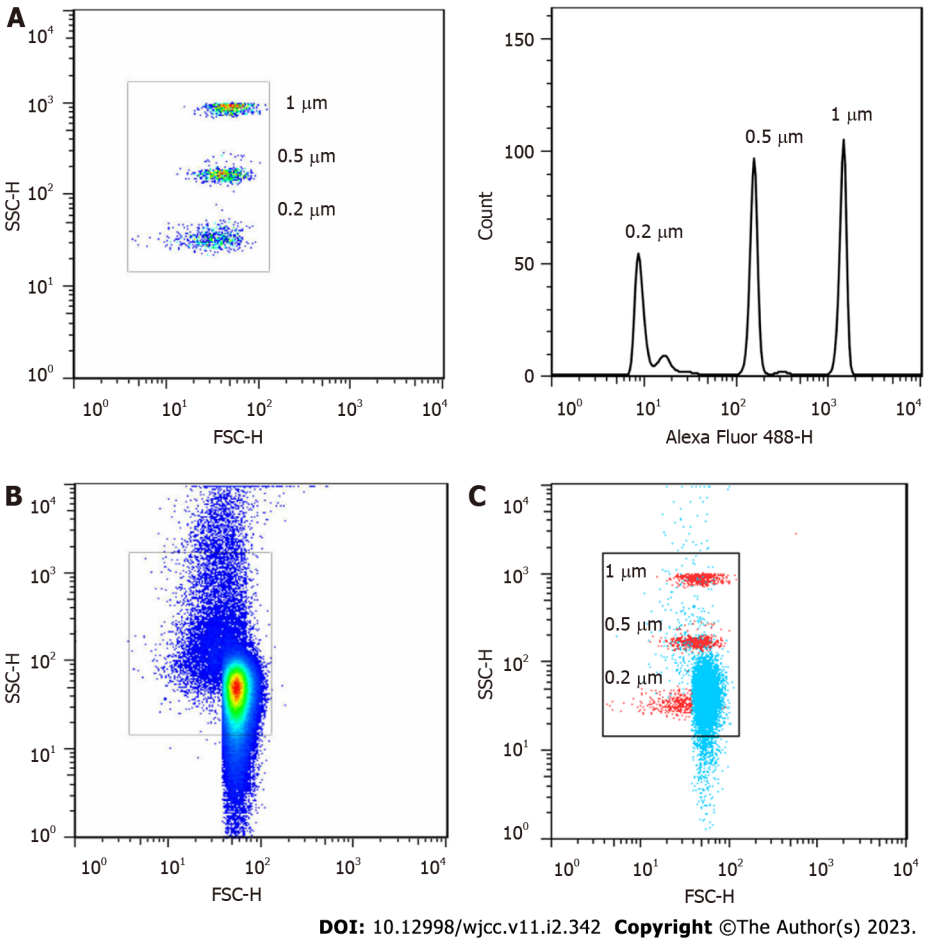

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Figure 1 Gating strategy for microvesicles and characterization of microvesicles isolated from human plasma. A: Gating strategy for microvesicles (MVs) based on calibration particles; B: Representative dot plots demonstrating the concentration of MVs isolated from human plasm; C: The merged dot plots of MVs isolated from human plasm (blue) and calibration particles (red).

sonication and reincubation with HUVECs significantly reduced the entry of MitoTracker-labelled MVsepsis into HUVECs (Figure 5) and reduced expression of *RSAD2*, *OAS2* and *CXCL10* (Figure 6). This result indicates that the mitochondrial content of MVsepsis is an important factor driving type I IFN signal activation.

DISCUSSION

In this study, we demonstrated that MVsepsis were abundant in mitochondrial content and that the levels of MVs and mitoMVs were significantly higher in patients with sepsis than in the healthy controls. MitoMVs were significantly correlated with TNF-α and sVCAM-1. MVsepsis, in particular, have the capacity to increase expression of type I IFN pathway members in HUVECs. This capacity was significantly reduced after destruction of mitoMVs by sonication. Collectively, mitoMVs constitute a subset of MVsepsis and may contribute to endothelial activation.

Mitochondria play important roles in energy metabolism, cell signal transduction, and apoptosis regulation. Therefore, mitochondria are one of the most easily affected cellular organelles in disease-induced dysfunction[23]. Therefore, characterizing mitochondria has increasingly become an important method to explore the pathogenesis of related diseases[24]. The most commonly used mediators are mitochondrial fluorescent probes, such as MitoTracker Deep Red, and antibodies against tom complexes, such as anti-tom22[25]. The former is chemically reactive and linked to thiol groups in the mitochondria[26]. Therefore, it is not affected by the mitochondrial membrane potential and is highly sensitive. The latter reacts with the tom complex *via* antigen–antibody interactions, which is specific and potentially indicates that mitochondrial proteins are present in an immunologically accessible form. In this study, the above two methods were used to label the mitochondrial content in MVs, and the results were positive. This provides reliable evidence that MVs isolated from human plasma carry mitochondrial content and suggests that the mitochondrial components in MVs exist in an immunologically accessible form.

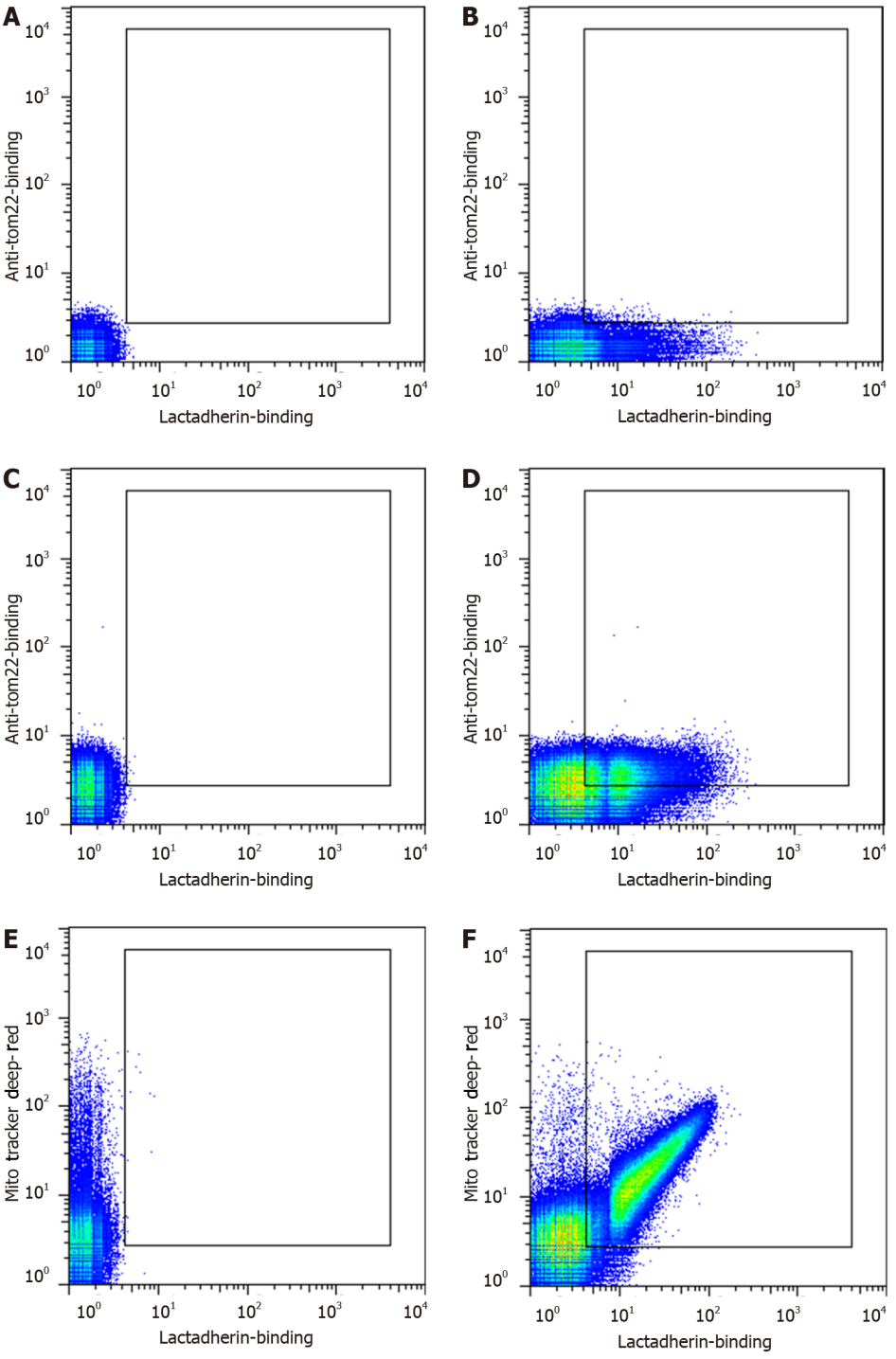

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Figure 2 Representative dot plots of circulating microvesicles from a patient with sepsis. Microvesicles (MVs) were labelled and analysed by flow cytometry. A: Unlabelled MVs (autofluorescence); B: MVs labelled with lactadherin-FITC; C: MVs labelled with anti-tom22-APC; D: MVs double stained with lactadherin-FITC and anti-tom22-APC; E: MVs labelled with MitoTracker Deep Red; F: MVs double stained with lactadherin-FITC and MitoTracker Deep Red.

Mitochondrial dysfunction contributes to several inflammatory diseases, ranging from sepsis[27] to rheumatoid arthritis[28]. Mitochondrial DAMPs, which are released by damaged mitochondria, have the ability to directly activate inflammatory responses[29]. In particular, Irene *et al*[30] showed that the MVs isolated from the sera of children with autism spectrum disorder not only contained mtDNA, one type of mitochondrial DAMP, but could also stimulate human microglia to secrete IL-1β. Similarly, we found mitoMVs. The expression of mitoMVs in patients with sepsis was significantly higher than that of the control group. Compared with the increase in MVs in the control group, the increase in mitoMVs in the sepsis group was more marked. This demonstrates that mitoMVs indicate the presence of sepsis and may participate in the immune response induced by sepsis.

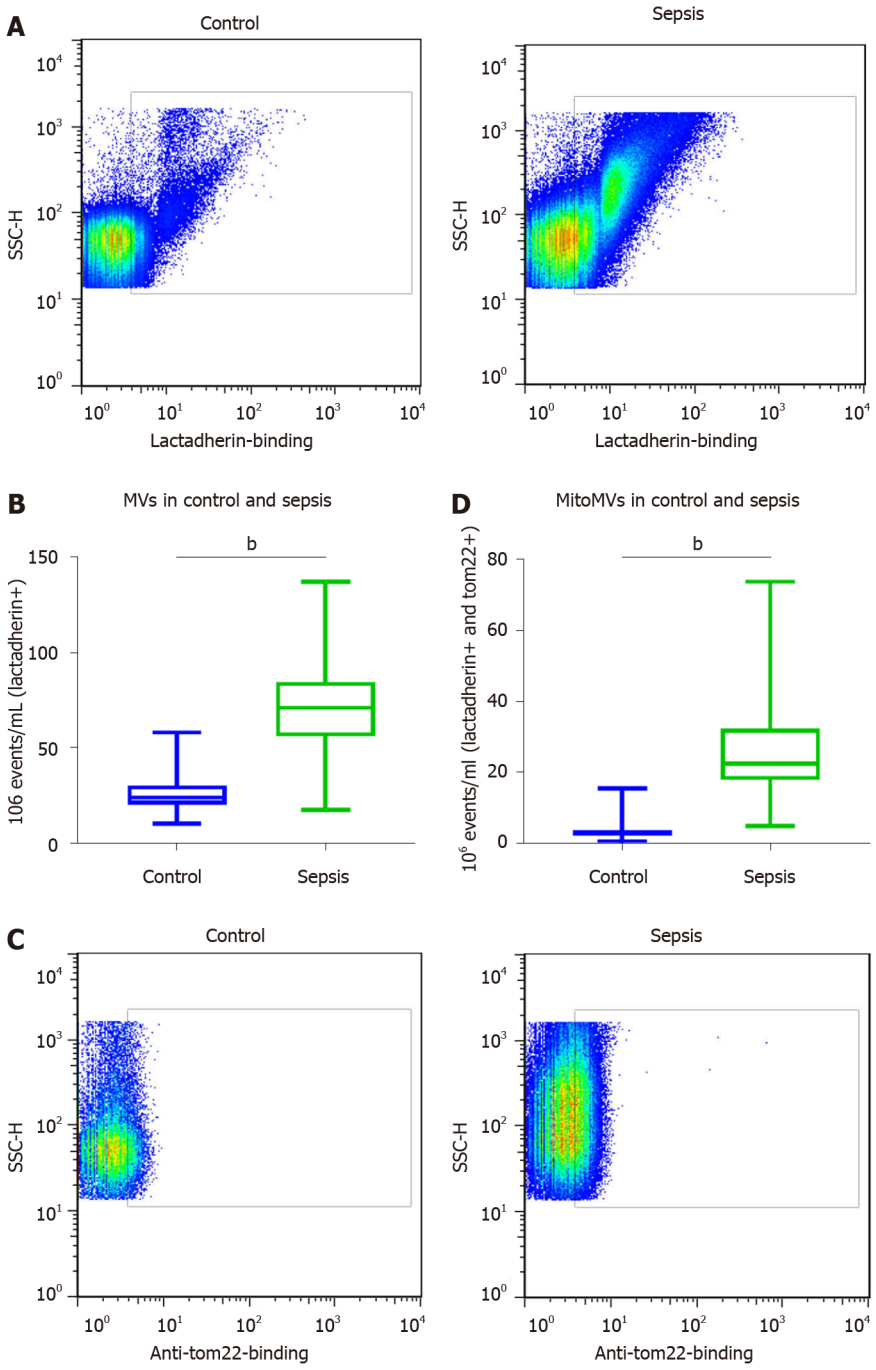

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Figure 3 Flow cytometric analysis of microvesicles and microvesicles carrying mitochondrial content. A: Representative dot plots of microvesicles (MVs) in patients with sepsis and healthy controls; B: Numbers of MVs in 19 patients with sepsis and 20 healthy controls; C: Representative dot plots of the microvesicles carrying mitochondrial content (mitoMVs) within the lactadherin+ population in patients with sepsis and healthy controls; D: Numbers of mitoMVs within the lactadherin+ population in 19 patients with sepsis and 20 healthy controls.

Previous studies have shown that the levels of various cytokines are elevated in sepsis[31,32] and can be used as markers of inflammation in sepsis[33]. Therefore, ELISA was used to detect expression of CRP, IL-6, IL-8 and TNF-α in the sera of patients with sepsis. Compared with those in the healthy control group, expression of the above inflammatory factors in the sepsis group were significantly higher. This confirms activation of the bodily inflammatory response in patients with sepsis. Correlation of MVs and mitoMVs with the above cytokines was analysed. MVs and mitoMVs were correlated with expression of TNF-α and mitoMVs were correlated with expression of sVCAM-1. This indicates that MVsepsis are potentially involved in sepsis-mediated immune activation and may mediate the immune response through endothelial activation. TNF-α is a strong proinflammatory cytokine[34] that participates in oedema formation, leukocyte adhesion to vascular ECs *via* the expression of adhesion molecules, and promotion of oxidative stress at sites of inflammation, and VCAM-1 regulates inflam-

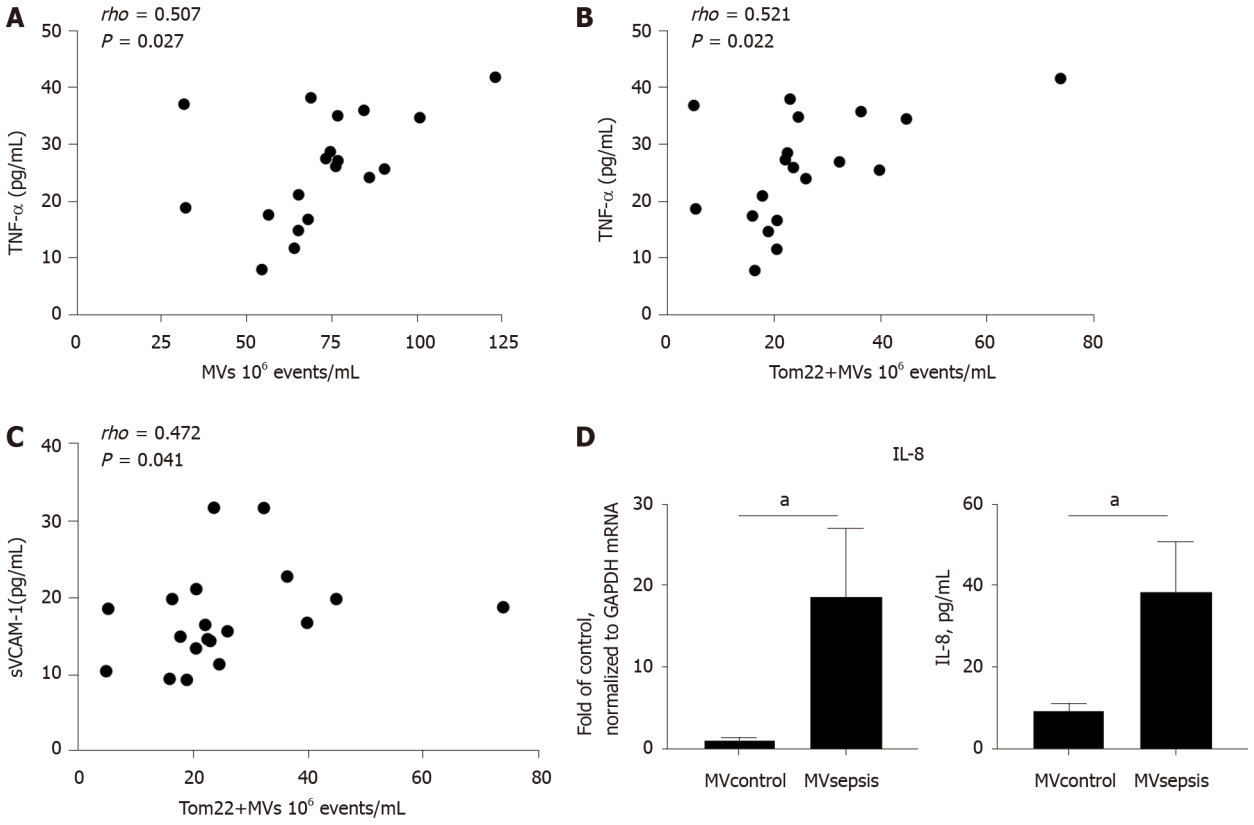

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Figure 4 Association between tumour necrosis factor-α, soluble vascular cell adhesion molecule-1 and microvesicles that were isolated from the plasma of patients with sepsis and induction of interleukin-8 in human umbilical vein endothelial cells. TNF-α: tumour necrosis factor-α; sVCAM-1: soluble vascular cell adhesion molecule-1; MVsepsis: microvesicles that were isolated from the plasma of septic patients; IL-8: interleukin-8.

mation-associated vascular adhesion and serves as a marker of endothelial activation[35].

MVs are the medium of information transmission between cells, and many studies have shown that MVs produced under pathological conditions have the ability to induce activation of recipient cells[18,36]. Therefore, based on the above inference, we explored the effect of plasma MVs on ECs *in vitro*. ELISA and qRT-PCR showed that compared with MVcontrol, MVsepsis increased expression of IL-8 in HUVECs. This result is similar to the findings of Hosseinkhani *et al*[37] that indicated that MVsepsis induced activation of ECs.

The type I IFN signalling pathway is related to inflammation[38] and is a manifestation of endothelial activation[39]. Several components of mitochondrial DAMPs can induce activation of type I IFN signals. In particular, increasing evidence shows that delivering MV cargo to recipient cells is an important way for MVs to exert their biological effects[21,40]. Therefore, the uptake of MVsepsis mitochondrial content and its ability to induce activation of type I IFN signals in HUVECs were investigated. MitoMVs were taken up by HUVECs, which accounted for the mechanism by which MVsepsis increased expression of type-I-IFN-dependent genes in HUVECs. This is similar to the study of Puhm *et al*[41]. They stimulated monocytes to produce mitoMVs *via* lipopolysaccharides, which are characteristic components of the Gram-negative bacterial cell wall, and these mitoMVs induced activation of type I IFN signalling in ECs. This study, together with our results, suggests that mitoMVs may be an effective target in sepsis-induced endothelial activation and for the treatment of sepsis in future. ECs with activated type I IFN signals have been shown to secrete adhesion molecules[42] and chemokines[43], which can amplify the activation and damage of ECs by inducing the adherence of monocytes[44] and neutrophils[45] to ECs. Many studies have shown a role for type I IFN signalling in vascular abnormalities associated with impaired blood vessel dilation. In particular, the latest research shows that type I IFN signals also mediate abnormal blood clotting induced by septic bacterial infection[46]. Finally, our results may also indicate that mitoMVs are not the only factor driving the elevated expression of type-I-IFN-dependent genes. Compared with MVcontrol, MVsepsis subjected to sonication still slightly promoted the expression of type I IFN signalling genes. Caielli *et al*[47] showed that mtDNA in its free form[48], which may not be completely eliminated during the process of MV isolation, can induce the activation of type I IFN signalling.

This study had some limitations. First, expression of genes that are representative of type I IFN signalling in HUVECs should be further assessed at the protein level. Second, human microvascular

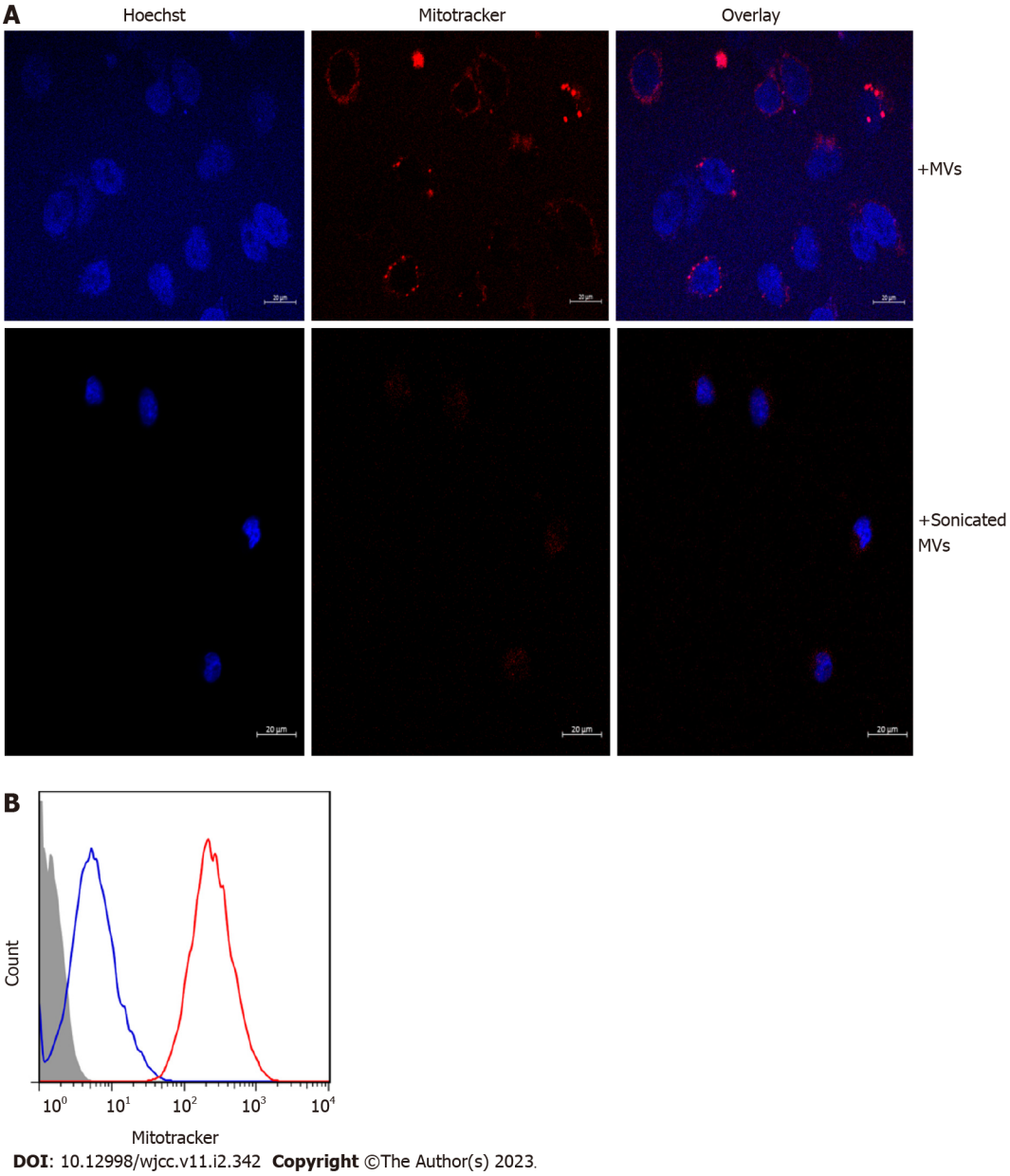

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Figure 5 Uptake of microvesicles carrying mitochondrial content by human umbilical vein endothelial cells before and after ultrasonic treatment. Microvesicles (MVs) were isolated from the plasma of patients with sepsis and labelled with MitoTracker Deep Red. A: Human umbilical vein endothelial cells (HUVECs) were incubated with the labelled MVs and treated or not treated with sonication. Nuclei were stained by Hoechst; B: Flow cytometric analysis of HUVECs after incubation with the labelled MVs either treated (blue) or not (red) treated with sonication.

endothelial cells, which are more relevant to the pathophysiology of sepsis than HUVECs, are not used to perform the *ex vivo* studies. Finally, since sonication does not only disrupt mitochondria, it is possible that other mitoMV components or nonmitochondrial contents induce type I IFN responses.

CONCLUSION

MitoMVs were increased in the plasma of patients with sepsis when compared with the healthy control group. The number of mitoMVs was correlated with inflammatory and endothelial activation markers. Moreover, mitoMVs from patients with sepsis induced expression of type-I-IFN-dependent genes in ECs. Therefore, circulating mitoMVs may have potential as a novel intervention target for sepsis-induced endothelial activation.

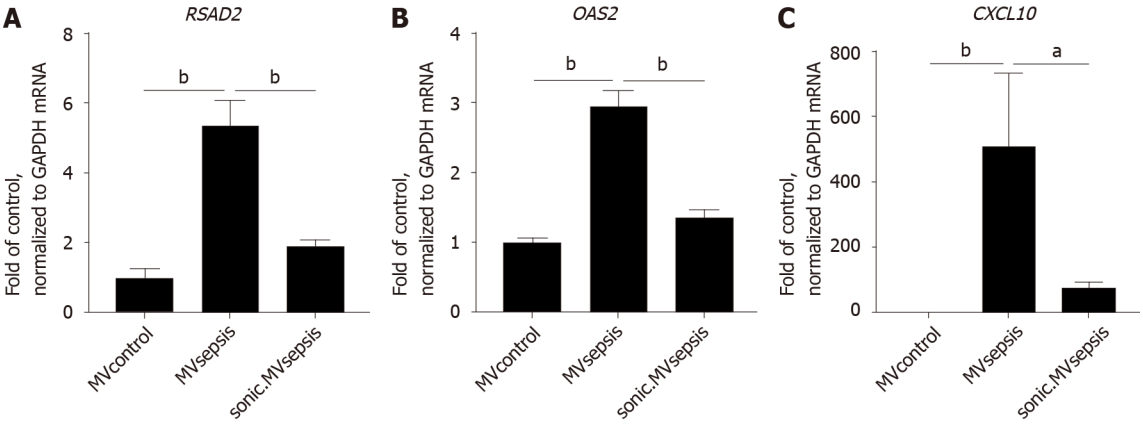

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Figure 6 mRNA expression in human umbilical vein endothelial cells after stimulation with circulating microvesicles. MVcontrol: microvesicles that were isolated from the plasma of healthy controls; MVsepsis: microvesicles that were isolated from the plasma of septic patients; sonic. MVsepsis: MVsepsis that were treated by sonication.

ARTICLE HIGHLIGHTS

Research background

Sepsis is a life-threatening complication of infection that involves endothelial injury that contributes to multiple organ failure. Microvesicles (MVs), which can transfer nucleic acids, organelles and proteins to target cells, are recognized as important mediators in intercellular communication.

Research motivation

MVs carrying mitochondrial content (mitoMVs) have been implicated in several diseases. However, it is not clear whether mitoMVs are involved in sepsis.

Research objectives

To explore whether mitoMVs constitute a subset of MVs isolated from plasma of patients with sepsis and contribute to endothelial activation.

Research methods

Confocal microscopy and flow cytometry were used to characterize the presence of mitoMVs and their expression in plasma. Human umbilical vein endothelial cells were stimulated with circulating MVs to evaluate their effect on endothelial activation.

Research results

MVs isolated from patients with sepsis were rich in mitochondrial content and the levels of MVs and mitoMVs were significantly higher in patients with sepsis than in healthy controls. The number of mitoMVs was positively associated with tumour necrosis factor-α and soluble vascular cell adhesion molecule 1. MitoMVs isolated from the plasma of patients with sepsis induced elevated expression of type-I-IFN-dependent genes in endothelial cells.

Research conclusions

MitoMVs were increased in the plasma of patients with sepsis and may activate the type I IFN signalling pathway in endothelial cells.

Research perspectives

MitoMVs may have potential as a novel interventional target for sepsis-induced endothelial injury.

FOOTNOTES

Author contributions: Zhang HJ participated in the study design, collected the samples, performed the experiments, and drafted the manuscript; Li JY helped to carry out the MV number experiments and analyze the data; Wang C helped to collect the samples and modify the manuscript; Zhong GQ conceived the study, participated in the study design, and helped to modify the manuscript; All authors read and approved the final manuscript.

Institutional review board statement: The study design was approved by the Ethics Committee of the First Affiliated Hospital of University of South China(protocol code 2020110323009).

Informed consent statement: Informed consent was obtained from all subjects involved in the study.

Conflict-of-interest statement: All the authors declare no conflict of interest.

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ORIGINAL ARTICLE

Retrospective Study

Is fascial closure required for a 12-mm trocar? A comparative study on trocar site hernia with long-term follow up

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Abstract

BACKGROUND

Despite the infrequency of trocar site hernias (TSHs), fascial closure continues to be recommended for their prevention when using a ≥ 10-mm trocar.

AIM

To identify the necessity of fascial closure for a 12-mm nonbladed trocar incision in minimally invasive colorectal surgeries.

METHODS

Between July 2010 and December 2018, all patients who underwent minimally invasive colorectal surgery at the Minimally Invasive Surgery Unit of Siriraj Hospital were retrospectively reviewed. All patients underwent cross-sectional imaging for TSH assessment. Clinicopathological characteristics were recorded. Incidence rates of TSH and postoperative results were analyzed.

RESULTS

Of the 254 patients included, 70 (111 ports) were in the fascial closure (closed) group and 184 (279 ports) were in the nonfascial closure (open) group. The median follow up duration was 43 mo. During follow up, three patients in the open group developed TSHs, whereas none in the closed group developed the condition (1.1% *vs* 0%, $P = 0.561$). All TSHs occurred in the right lower abdomen. Patients whose drains were placed through the same incision had higher rates of

TSHs compared with those without the drain. The open group had a significantly shorter operative time and lower blood loss than the closed group.

CONCLUSION

Routine performance of fascial closure when using a 12-mm nonbladed trocar may not be needed. However, further prospective studies with cross-sectional imaging follow-up and larger sample size are needed to confirm this finding.

Key Words: Trocar site hernia; Port site hernia; Fascial closure; Laparoscopic colorectal surgery; Nonbladed trocar

Core Tip: The incidence of trocar site hernias (TSHs) varied from 0.1% to 2%. Previous studies and guidelines have also suggested fascial closure when using a > 10-mm trocar. The findings from this study demonstrated no significant difference in the incidence of TSHs between facial closure and nonclosure groups (0% *vs* 1.1%, $P = 0.561$) when the median clinical follow-up duration was 41 mo. Therefore, fascial closure may be selectively omitted when using a 12-mm nonbladed trocar.

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INTRODUCTION

Minimally invasive surgical approaches have gained acceptance worldwide, given their superior benefits in terms of postoperative recovery and wound healing. However, certain complications can occur following laparoscopy, including trocar site hernias (TSHs), the incidence of which varies from 0.1% to 2%[1,2]. Clinical presentation of patients can range from asymptomatic to bowel strangulation in case of delayed diagnosis[3]. Despite the multifactorial etiology of this condition, older age, obesity, and wound infection have been identified to be the predisposing factors[4-6]. Several studies have also suggested fascial defect closure when using a ≥ 10-mm trocar[7-9]. Hence, emphasis should be placed on this preventable condition in high-risk patients.

Similarly, minimally invasive colorectal surgeries have become the standard treatment approach at many centers. Indeed, laparoscopy facilitates meticulous dissection and bowel transection using staplers. Equivalent long-term oncologic outcomes could be achieved by minimizing postoperative morbidities and promoting early recovery of bowel function[10-12]. During the procedure, 12-mm ports are commonly used for 10-mm clips or stapler application. Unlike routine midline incision closure, fascial closure of a 12-mm port incision remains optional. Therefore, we aimed to evaluate the necessity of fascial closure of the 12-mm nonbladed trocar incision made during colorectal surgeries.

MATERIALS AND METHODS

Study design

This single-center retrospective study was approved by the Siriraj Institutional Review Board (Protocol No. 900/2562). Data were collected from July 2010 to December 2018.

Patients

All patients aged ≥ 18 years who underwent nonurgent minimally invasive colorectal surgery at the Minimally Invasive Surgery Unit of Siriraj Hospital, Mahidol University, Thailand, were included. Patients who had incomplete medical records, had connective tissue disease, underwent different fascial closure methods, required conversion to open surgery, < 12 mo of follow up, and did not undergo postoperative cross-sectional imaging were excluded.

Procedures

We entered the abdominal cavity from the periumbilical region using Hasson's open technique for laparoscopic surgery or mini-midline incision for hand-assisted laparoscopic surgery to create a pneumoperitoneum. A 12-mm nonbladed trocar was then inserted at a nonperiumbilical location according to the type of surgery. After completing the laparoscopic phase, a mini-midline incision that extended from the periumbilical incision was created for specimen retrieval. A 10-mm abdominal drain was then placed, as specified by the intraoperative findings. The abdominal fascia at the midline incision was closed using a continuous absorbable suture. Closure of the 12-mm trocar site was optional and depended on the surgeon's preference. The techniques included direct suture with absorbable material and closure under laparoscopic direct vision using the suture passer needle technique. Because of the retrospective nature of our study, details regarding TSHs and repair techniques could not be clearly determined. All patients were followed up using cross-sectional imaging based on the primary disease.

Outcome measurement

The clinicopathological characteristics of the patients, including age, sex, body mass index, diabetes mellitus, benign prostatic hyperplasia, American Society of Anesthesiologists physical status classification, Modified Charlson Comorbidity Index, serum albumin level, creatinine level, disease diagnosis, type of operation, and number and location of the 12-mm port, were reviewed. The primary outcome was the incidence of TSHs in the nonperiumbilical area, which was diagnosed with postoperative clinical examination or cross-sectional imaging. The date of diagnosis and further management were recorded. Furthermore, details regarding the primary surgery, complications according to the Clavien–Dindo classification[13], and incidence rates of incisional and parastomal hernia were also assessed.

Statistical analyses were performed using SPSS statistical software version 21. The variables were expressed as number (%), mean ± SD, and median with interquartile range (IQR). The data were analyzed using student's t-test, Mann–Whitney U test, and chi-square test. TSH incidence was analyzed using the Kaplan–Meier curve and log-rank test. P values < 0.05 indicated statistical significance.

RESULTS

A total of 537 patients with colorectal diseases underwent minimally invasive colorectal surgery. After applying the exclusion criteria, 254 patients (390 ports) were ultimately included in the study. To facilitate comparison, we categorized 70 patients (111 ports) into the fascial closure (closed) group and 184 (279 ports) into the nonfascial closure (open) group (Figure 1). Both groups had comparable baseline characteristics and operative details, except for a higher body mass index in the open group. Table 1 summarizes the clinicopathological characteristics of the patients.

Three patients (3/279 ports, 1.1% *per* port) in the open group developed TSHs, whereas none in the closed group developed TSHs (0/111 port, 0% *per* port). There was no significant difference in the incidence of TSHs between the two groups (P = 0.561). The median clinical follow-up duration was 41 mo (IQR 25, 63), whereas the median cross-sectional imaging follow-up duration was 31 mo (IQR 20, 51). Figure 2 demonstrates the Kaplan–Meier analysis of TSH events. Three patients with TSHs were women with adenocarcinoma of the colon who underwent anterior resection. Surveillance computed tomography found that all such patients developed TSHs in the right lower quadrant area containing omental fat. The time to diagnosis ranged from 13 to 34 mo. One patient underwent elective hernia repair at another hospital. Table 2 lists the clinical data. Moreover, one of the three patients developed a concomitant asymptomatic incisional hernia at the midline incision. There were no significant correlations between TSHs and incisional hernia (P = 0.19). None of the patients with TSHs underwent stoma creation during the primary surgery. Subgroup analysis showed that the incidence of TSHs was slightly higher in patients with drain placement than in those without drain placement (3.1% *vs* 0.5%, P = 0.371).

The open group showed shorter operative time and lower blood loss than the closed group. Moreover, the open group experienced significantly lower fitted postoperative pain at 6, 12, 24, and 48 h (P = 0.018) (Figure 3). The length of the hospital stay was comparable between the two groups. No significant difference in complications, such as surgical site infection, anastomosis leakage/bleeding, small bowel obstruction, ileus, arrhythmia, electrolyte imbalance, and urinary tract infection, was observed. In our study, surgical site infection occurred at the midline incision (Table 3).

DISCUSSION

At present, laparoscopic surgery is a globally acceptable approach across many fields of surgery. Unfortunately, the development of postoperative TSHs remains one of its specific complications. Although prior studies have reported the rare incidence of TSHs after surgery, this complication can be

Table 1 Clinicopathological characteristics

	Closed (*n* = 70)	Open (*n* = 184)	*P* value
Age	63 ± 12	63 ± 11	0.461
Male sex	38 (54.3)	100 (54.3)	0.993
Body mass index (kg/m2)	23 ± 3	24 ± 4	0.024
Diabetes mellitus	12 (17.1)	44 (23.9)	0.245
Benign prostatic hyperplasia (*n* = 138)	3 (7.9)	9 (9.0)	1.000
ASA classification			0.634
1	13 (18.6)	29 (15.8)	
2	47 (67.1)	120 (65.2)	
3	10 (14.3)	35 (19.0)	
Modified CCI score	4 (3.6)	4 (3.6)	0.958
Albumin ≥ 3 g/dL	59 (85.5)	156 (88.1)	0.581
Creatinine ≥ 2 mg/dL	2 (2.9)	5 (2.7)	1.000
Disease diagnosis			0.327
Benign	0 (0)	5 (2.7)	
Malignancy	70 (100)	179 (97.3)	
Operations			0.193
Right hemicolectomy	7 (10)	28 (15.2)	
Left hemicolectomy	29 (41.4)	57 (31.0)	
Subtotal colectomy	0 (0)	1 (0.5)	
LAR/APR	32 (45.7)	97 (52.7)	
Total proctocolectomy	1 (1.4)	0 (0)	
Others	1 (1.4)	1 (0.5)	
Numbers of 12-mm port *per* person			0.511
1	29 (41.4)	90 (48.9)	
2	41 (58.6)	93 (50.5)	
3	0 (0)	1 (0.5)	

ASA: American Society of Anesthesiologists; CCI: Charlson Comorbidity Index; LAR: Laparoscopic anterior resection; APR: Abdomen perineal resection.

Table 2 Clinical data of three patients with trocar sire hernia

	Age	BMI	ASA	Alb	Cr	Disease location	Operation	Drain	Time to diagnosis	Treatment
1	77	19.9	3	2.9	2.4	Rectosigmoid	HALS	No	34 mo	None
2	59	29.7	2	4.3	0.5	Sigmoid	Laparoscopic	RLQ	13 mo	Open repair
3	72	23.4	3	4.6	1.3	Sigmoid	HALS	RLQ	31 mo	None

BMI: Body mass index (kg/m^2); Alb: Serum albumin level (g/dL); Cr: Serum creatinine level (mg/dL); HALS: Hand-assisted laparoscopic surgery; RLQ: Right lower quadrant.

avoided with proper intraoperative management. The predisposing factors for developing hernias may comprise both patient-related instrument-related factors[3,14]. To improve the surgical outcomes and lessen the incidence of TSHs, modifications to the laparoscopic trocar tip have been attempted. Indeed, one study showed that a bladeless trocar allows tissue penetration without cutting the abdominal muscle fibers, which reduces trocar site bleeding and overall complications[15]. However, some laparoscopic instruments may require trocars with larger diameters as working ports. Nonetheless, routine

Table 3 Secondary outcomes

	Closed (*n* = 70)	Open (*n* = 184)	*P* value
Operative time (minute)	170 (110, 240)	123 (100, 185)	0.004
Estimated blood loss (mL)	50 (30, 11)	30 (20, 100)	0.011
Length of hospital stay (day)	5 (5, 7)	5 (4, 6)	0.122
Complications			0.228
CD-1	6 (8.6)	9 (4.9)	
CD-2	7 (10)	10 (5.4)	
CD-3	2 (2.9)	3 (1.6)	
CD-4, 5	0	0	

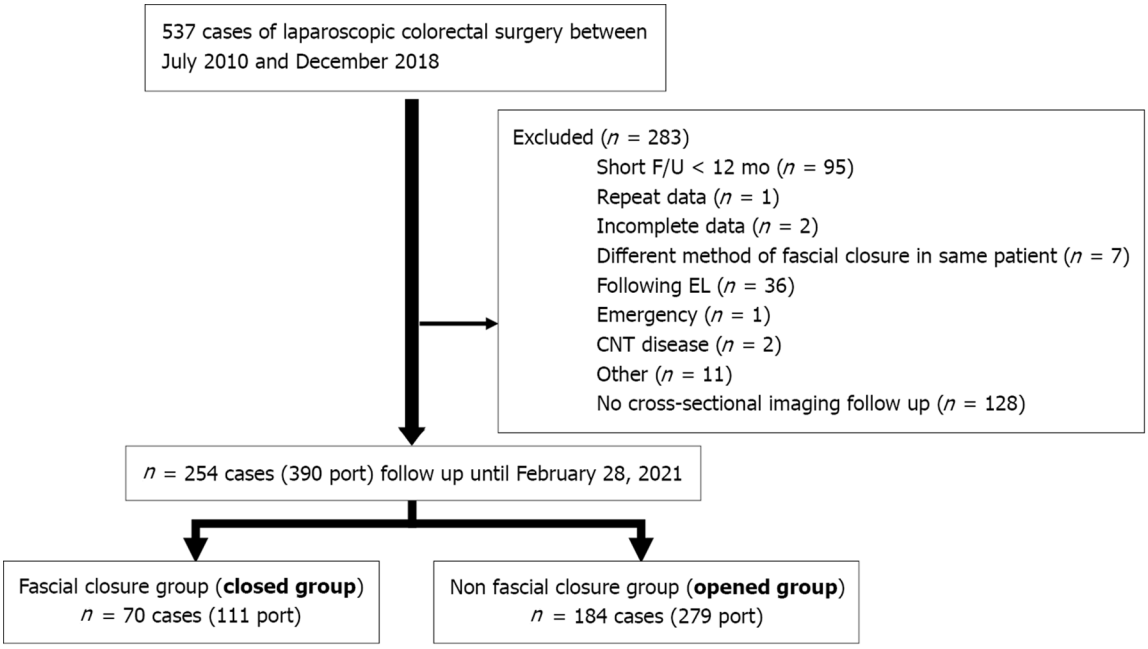

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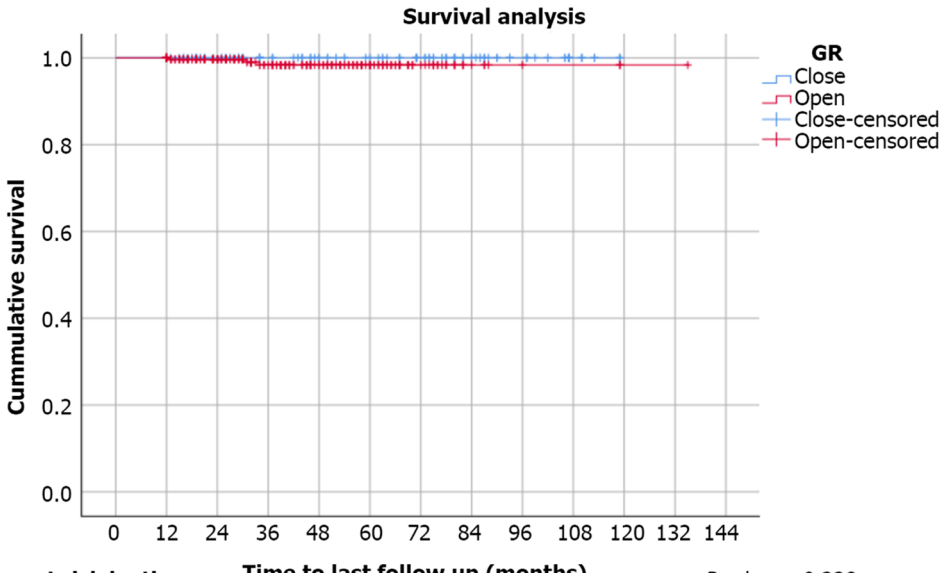
Figure 1 Flowchart of analysis. EL: Exploratory laparotomy; CNT: Connective tissue; F/U: Follow up.

closure of these fascial defects remains controversial. Owing to the potentially harmful consequences, some studies have recommended closing the defect when using a 10-mm trocar[3,16].

Previously, prospective data on other laparoscopic procedures have proven the safety and feasibility of leaving the fascia open after the application of a 10-mm trocar[17]. Our study mainly aimed to determine the necessity of the fascial closure of a 12-mm trocar after minimally invasive colorectal surgeries. Our results demonstrated that routine closure provided no significant benefit. The incidence of TSHs observed in our series was 1.1%, which was comparable to that stated in other reports. All cases underwent cross-sectional imaging based on the index diagnosis. We believe that reliable results were achieved, given that computed tomography is considered one of the best methods for occult hernia detection[18,19]. In 2004, Tonouchi *et al*[9] classified TSHs into three types. All three cases of TSHs included in this study were of late-onset type. No bowel obstruction or strangulation occurred during the follow-up. Concerning the precipitating factors, only advanced age was found in two patients. None of them were obese or had prior wound infections at the trocar site. Moreover, Sakamoto *et al*[20] found TSHs after laparoscopic colectomy in elderly patients with low body mass index. Frailty may lead to decreased abdominal wall strength over time. Furthermore, another study found a relationship between TSH incidence and abdominal drain placement. Based on these findings, all patients with TSH also underwent drain placement at the same location of the TSHs after the trocar was removed intraoperatively[20].

Regarding other postoperative results, this study indicated that nonfascial closure, in particular, yielded several advantages. Closure defect usually takes time and may prolong the duration of operation[2]. Postoperative pain is also greater with transfascial suture. However, these parameters may



Number at risk by time **Time to last follow up (months)** *P* value = 0.228

Time to last follow up (months)	12	24	36	48	60	72	84	96	108
Close	110	95	75	65	57	47	32	19	6
Open	278	210	142	95	58	26	7	3	3

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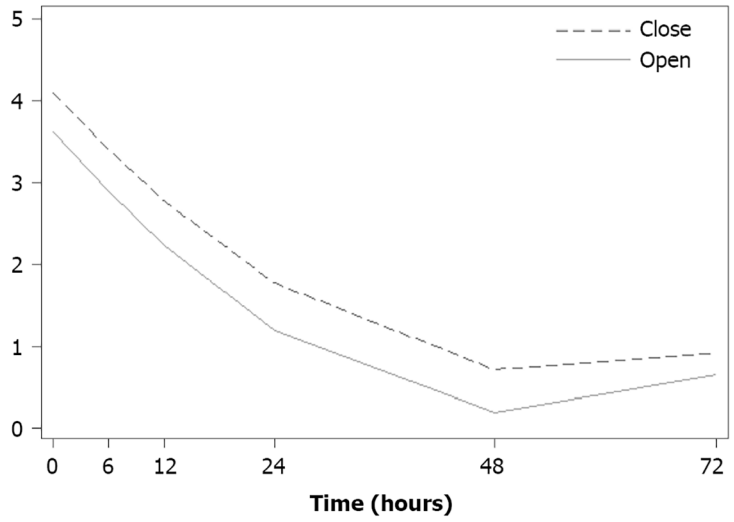
Figure 2 Kaplan–Meier analysis of trocar site hernia events. GR: Group.



Time (hours)	0	6	12	24	48	72	All
P value	0.177	**0.076**	**0.034**	**0.017**	**0.009**	**0.279**	**0.0179**

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Figure 3 Fitted postoperative pain.

be confounded by various factors. Operative time varies owing to cancer staging or degree of adhesion in benign diseases. The amount of blood loss may be attributed to intraoperative findings or surgical techniques.

Another limitation of our study is its retrospective design. Details regarding the TSHs and repair techniques could not be clearly determined. Given the low TSH rates in our population, factors associated with TSH occurrence could not be identified. Moreover, there was no patient with TSH in the closed group, whereas, 1.1% of TSH was identified in the open group. There was no statistical significance in this study. Further prospective studies with cross-sectional imaging follow-up and larger sample size should be conducted to confirm whether the outcomes of nonfascial closure are not inferior to those of fascial closure.

CONCLUSION

Fascial closure may be selectively omitted when using a 12-mm nonbladed trocar. To achieve greater benefit from minimally invasive surgery, optimal intraoperative evaluation and decision making are mandatory for TSH prevention.

ARTICLE HIGHLIGHTS

Research background

The incidence of trocar site hernias (TSHs) varies from 0.1% to 2%. Several studies have also suggested fascial defect closure when using a ≥ 10-mm trocar, especially for midline incision and bladed trocar.

Research motivation

The findings from this study imply that there is no significant difference in TSH between the closure and nonclosure groups for 12-mm nonbladed trocar. However, further prospective studies with a larger sample size are required.

Research objectives

To identify the necessity of fascial closure for a 12-mm nonbladed trocar incision in minimally invasive colorectal surgeries.

Research methods

Closure or nonclosure was decided based on the surgeon's preference. All patients were followed up *via* cross-sectional imaging based on the primary disease.

Research results

Three patients in the open group developed TSHs, whereas none in the closed group developed TSHs (1.1% *vs* 0%, $P = 0.561$). The open group had a significantly shorter operative time and lower blood loss than the closed group.

Research conclusions

Fascial closure may be selectively omitted when using a 12-mm nonbladed trocar.

Research perspectives

Further prospective studies should be conducted with a larger sample size.

FOOTNOTES

Author contributions: Trakarnsanga A conceived the study, revised the manuscript, and participated in its coordination; Krittiyanitsakun S and Nampoolsuksan C participated in the database collection and drafted the manuscript; All authors read and approved the final manuscript.

Institutional review board statement: This single-center retrospective study was approved by the Siriraj Institutional Review Board (SIRB Protocol No. 900/2562).

Informed consent statement: All of the patient consents give Associated Professor Atthaphorn Trakarnsanga MD. and his team at Minimally Invasive Unit, Department of Surgery, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand permission to publish reproduce and distribute, the attached case study, regarding trocar site hernia. The authors aware that the case study does not mention patient name, address but it does reflect patient medical care, gender, age, and medical history. All of the patients will not be paid in any manner for use of the case study as described above. They will not receive any royalties or other compensation in connection with any suck publication or use. All of the patients are not required to sign the consent form, and they may refuse to do so. Their medical treatment and payment for healthcare will not be affected by whether or not they sign the consent form. They may withdraw these consents for any future sharing at any time by notifying the research team, but their withdrawal will not affect information that has already been shared or published. This authorization has no expired date.

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Data sharing statement: The dataset utilized during the current study is available within the institutional collected data system that was used under Siriraj's institutional review board committee approval for this study. Data are

available upon reasonable request with permission of Siriraj's institutional review board committee.

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ORIGINAL ARTICLE

Retrospective Study

Ten-year multicentric retrospective analysis regarding postoperative complications and impact of comorbidities in hemorrhoidal surgery with literature review

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Abstract

BACKGROUND

Hemorrhoidal disease (HD) is considered a low-severity pathology by both general population and physicians, but the lengthy conservative therapy and postoperative complications suggest otherwise.

AIM

To assess the effectiveness of different treatment options, both conservative and surgical, in contrast with some preexisting comorbidities.

METHODS

We conducted a retrospective, 10-yearlong study between January 2011 and December 2021 in two surgical centers, a private and a state-owned hospital. We compared the efficacy and safety of several treatment options, such as open hemorrhoidectomy, stapled hemorrhoidopexy, rubber band ligation and infrared coagulation in terms of complication rates and types and their correlation with different preexisting comorbidities such as inflammatory bowel disease (IBD), use of anticoagulant medication (AM) and liver cirrhosis. We also conducted a 20-years long PubMed research (1.263 articles) for relevant comparisons.

RESULTS

Our study recorded 10940 patients with HD, 10241 with conservative and 699 with surgical treatment. Out of these, the male-to-female ratio of 1.3, and a peak in age distribution between 59 and 68 years old (32% of patients). For the entire study, we recorded a 90% incidence of immediate pain, immediate bleeding in 1.5% (11 cases), delayed bleeding in 1.0% (7 cases), and 0.6% surgical site infections. Urinary retention was also present, with 0.2% of patients, anal stricture in 1% and fecal incontinence for 0.5% of patients (4 cases). We recorded no severe complications such as Fournier`s gangrene or rectovaginal perforations. IBD accounted for 6% of the patients, with ulcerative colitis in 12% and Chron`s disease in 10.5%. 6.6% of the patients had AM, determining 4% immediate and 2% delayed bleeding, in surgically treated patients.

CONCLUSION

Our study determined that most common complications (pain, urinary retention, bleeding, and stricture) are correlated with each surgical technique and pre-existing comorbidities.

Key Words: Retrospective; Hemorrhoidal; Postoperative; Complications; Comorbidities

Core Tip: We compared the efficacy and safety for the most widely used surgical and non-surgical solutions for hemorrhoidal pathology treatment, such as hemorrhoidectomy, stapled hemorrhoidectomy, rubber band ligation (RBL), sclerotherapy, and infrared coagulation (IRC) in terms of complication rates, types of complications and implication of different preexisting comorbidities such as inflammatory bowel disease, use of anticoagulant medication and liver cirrhosis. We determined that even if RBL, RBL and IRC or IRC alone usually only require a one-day admission model, the classic or modified Milligan-Morgan technique still provides better overall long-term results, despite initially determining a higher level of pain and bleeding.

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INTRODUCTION

Although hemorrhoidal disease (HD) has been described many centuries ago (documented evidence in Mesopotamian literature as old as 1500 BC), a worldwide study to address the overall incidence and prevalence across different races, cultures, and socio-economic levels has not yet been published[1]. While in United States, hemorrhoidal pathology seems to be ranking forth amongst all gastrointestinal diseases that drive the patients to hospitals, especially to day-care clinics, determining more than 3 million admissions per year (according to a review by Everhart *et al*[2] in 2009), in other parts of the world, such as Eastern and Central Europe, the prevalence rate is close to 11%, as the Sheikh *et al*[3] online web-based survey shows.

Even though many studies concur that the bulk of the patients have low-severity stages of hemorrhoidal disease during the first clinical presentation, if we factor in its high prevalence rate, of more than 10% of the entire adult population, the rather long time for the conservative medication-based therapy to produce clinically significant results and the severity of complications after surgery, it becomes clear that this pathology has a great overall impact on patients[4-7].

MATERIALS AND METHODS

Our study is a bi-centric, 10-year-long retrospective analysis, conducted both in a private clinic as well as in a state-owned hospital. The Colorectal Department of MedLife Hospital S.A., (Clinic A), is the private clinic, a one-day-surgery type of medical practice, the state-owned one is Witting Clinical Hospital, Department of General Surgery, a university multidisciplinary unit (Clinic B), that is focused more on a multi-day admission setting for patients, including HD.

Between January 2011 and December 2021, a total of 10940 patients from both clinics with the diagnosis of HD on various degrees, that needed conservative or surgical treatment were selected, according to inclusion criteria.

Inclusion criterion consisted in patients diagnosed with primary hemorrhoidal disease with indication for treatment, regardless of their age, sex, comorbidities, and length of hospitalization; comply with at least one of the scheduled postoperative follow-ups, at 7 d, 14 d and 30 d, respectively.

Exclusion criteria consisted in patients consulted in the outpatient care that needed no treatment at all, patients with secondary hemorrhoidal pathology as the primary diagnosis as a direct expression of portal syndrome with origins other than liver cirrhosis (LC) and with important collateral venous drainage, patients skipping at least one of the scheduled follow ups and patients that had corrective procedures in other medical facilities after the initial surgery in our clinics.

For clinical diagnosis of HD, we used the standard 4 stage Goligher`s classification that also served as a tool to differentiate the choice of treatment options.

The study recorded details such as age, sex, urban or rural environment, classification of hemorrhoidal pathology before surgery, comorbidities with impact on HD, type and length (in minutes) of surgical procedure, duration of hospitalization (HT), return to work time (RTW), type of complications developed and their time of onset, in respect to the initial procedure.

Types of procedures recorded were open hemorrhoidectomy with a modified Milligan Morgan technique (MOH), stapled hemorrhoidopexy (SH) and rubber band ligation (RBL) with infrared coagulation (IRC). For comparison purposes we also described or experience with open hemorrhoidectomy by ligasure and Doppler guided hemorrhoidectomy. We had no cases operated with any of the closed hemorrhoidectomy techniques (CH).

Regarding the postoperative complications, our study recorded the most significant ones, such as pain, bleeding, infections of the surgical site (such as perianal abscesses and pelvic abscesses), mechanical complications (such as rectal or vaginal perforations), anal stricture, fecal incontinence, and urinary retention.

To assess the pain intensity, we used the standard Visual Analogue Scale (VAS) with 0 points for no pain and 10 points for extremely severe pain. Immediate postoperative pain was evaluated every 4 h, 8 h, and 24 h respectively and for the delayed postoperative pain we used the 7 d, 14 d and 30 d markers respectively. Follow-up visits were scheduled according to these markers.

Bleeding was evaluated in a qualitative manner, with number of sponges/gauzes need to achieve hemostasis, both during the surgical procedure as well as in the postoperative stage, at 1 day and 7 d respectively (for delayed hemorrhage).

As for comorbidities, the study focused just on those with documented relation and impact for HD that can be managed in non-emergency centers, such as inflammatory bowel disease (IBD), anticoagulant medication (AM), and LC.

Inflammatory bowel disease recorded both Crohn`s disease (CD) as well as ulcerative colitis (UC), being the most met in medical practice. In this category we merged both chronic evolving IBD as well as newly discovered pathology.

The classes of anticoagulant medication recorded were antithrombotic (AT), such as Clopidogrel (Plavix), and anticoagulants (AC), including all classes of novel oral AC (NOAC) such as rivaroxaban

(Xarelto), dabigatran (Pradaxa) and apixaban (Eliquis).

LC was recorded solely as a preexisting, documented diagnosis and in no connection to the ethiopathogenic mechanism (viral, medication-induced, toxic, or alcoholic, *etc.*). As such we did not differentiate between primary biliary cirrhosis or alcohol and medication-induced LC.

For results comparing, a narrative literature review was carried out of all significant scientific papers published in PubMed database during the last twenty years (2002-2022). These results then served as a comparison with our study, and key differences were highlighted.

All details were integrated into an Excel database. Standard statistical reports have been created using the Excel included tools. For advanced statistical analysis we used IBM`s SPSS, Statistics Campus Editions version (SPSS Inc., Chicago, IL, United States) with university account (https://www.ibm.com/products/spss-statistics-campus-editions).

Kolmogorov-Smirnov and Shapiro-Wilks test were used for determining the homogeneity of the variances with Levene test for normality distribution evaluation. For continuous variables we used the *t* test for 2 group mean comparisons with the paired *t* test for dependent 2 group mean comparisons. In addition, the Mann-Whitney U test was chosen for independent groups comparisons with Wilcoxon signed rank test for dependent groups. For comparing more than 2 groups of normally distributed data we run the ANOVA test and for non-normally distributed data the Kruskal-Wallis test was used. Statistical significance value was set for $P < 0.05$.

RESULTS

Between January 2011 and December 2021, both clinics recorded a total of 10940 patients diagnosed with HD. From those, 8144 patients (74%) received conservative, medication-based treatment and 2796 have been treated either with or minimally invasive procedures (2097 patients) or with invasive techniques (699 patients). This lot of 2796 patients will be further discussed during this study. The complete distribution of patients, according to clinics and types of procedures is in Table 1.

Literature review consisted in a custom interrogation of PubMed and PubMedCentral for the terms "hemorrhoid" and "postoperative" and "complications", for the past 20 years (2002-2022), selecting clinical trials (CT), meta-analysis (MA), randomized control trials (RCT), reviews (RW), and systematic reviews (SR) as scientific sources, resulting in a list of 1263 articles. From those, CT accounted for 611, MT for 204, RCT for 423, RW for 529 and SR for 212. The list was sorted by newer articles first, then by SR, RW and MA with RCT and CT being last; also, only English redacted papers have been reviewed. From this pool of articles, we further refined the search by using pair of terms for each topic of our study, such as "hemorrhoidectomy" and "inflammatory bowel disease" that rendered a total of 9 results, "hemorrhoidectomy" and "anticoagulant medication" 2 results, and "hemorrhoidectomy" and "cirrhosis" 5 results, within the same timeframe.

The demographic analysis shows 1620 male patients and 1176 female patients (1.3 M/F ratio), the peak number of cases per age group being in the range of 39-48 years, with 340 cases (29%). The complete demographic characteristics of the lot is displayed in Table 2. There was no difference between the groups in terms of demographic data ($P > 0.05$) (Table 2).

As stated, the standard 4-grade Goligher`s classification of HD was selected for diagnosis, by both clinics. However, the indication for treatment was guided by the actual clinical status of each individual patient, as many presented with a combination of HD grades (Table 3).

Therefore, the complete distribution of treatment options according to the grading of HD is as follows: All grade I patients, 8144 (74%) received conservative therapy (diosmine-based medication, sitz baths, topic agents with galenic medication, *etc.*); all patients with grade II HD and all patients with grade II that also had at least one grade III hemorrhoidal dilation plus all grade III patients received non-surgical treatment with RBL and IRC (2097 cases, 19%). All patients with grade III HD that also had at least one grade IV dilation, and all fully grade IV patients were automatically assigned for surgical treatment consisting of OH, SH or OH with ligasure (Valleylab, Boulder, Colorado, United States) (699 cases, 6%).

The range of surgical procedures was different amongst the clinics. Both clinics performed OH, SH and rubber band ligation (RBL) with infrared coagulation (IRC) in the same surgical session, the latter two being always performed in conjunction and never as a stand-alone procedure. However, in Clinic B, we also had the option to use hemorrhoidectomy by means of high-energy auto-sealing electrocautery devices, such as ligasure (for the first 5 years in the study, using only the Atlas platform, as the newer FX and LS were not available at that time).

The OH technique used in both clinics is a modified Milligan-Morgan procedure that makes use of an electrocautery scalpel with blended current setting (35 W of peak power) for streamlining each hemorrhoidal dilation prior to a transfixing ligation with poly-filament 2/0 thread, round tip needle, followed by resection with at least 5 mm safe margin from ligation.

Doppler-guided hemorrhoidal artery ligation (DG-HAL) became available in the private clinic, only in the last 4 mo of our study, totaling 34 patients that were not included in this lot. The initial clinical results, although being particularly good and promising, due to the substantial number of discrepancies

Table 1 Distribution of patients according to clinics and procedure types

Type of treatment	Both clinics	Clinic A (*n*)	Clinic A (%)	Clinic B (*n*)	Clinic B (%)
Conservative	8144	7737	95	407	5
Minimally invasive	2097	1657	79	440	21
Surgical treatment	699	210	30	489	70

Table 2 Complete demographic details of the recorded lot

Criteria	Age group	Females				Males			
		Rural		Urban		Rural		Urban	
		n	%	*n*	%	*n*	%	*n*	%
Gender	19-28	4	2	60	6	20	5	36	3
	29-38	28	15	204	21	76	20	340	28
	39-48	32	17	308	31	156	40	392	32
	49-58	32	17	216	22	68	18	152	12
	59-68	60	32	140	14	48	12	188	15
	69-78	20	11	48	5	20	5	84	7
	79-88	12	6	12	1	-	-	36	3
	89-98	-	-	-	-	-	-	4	0.1

Table 3 Classification of cases, according to grades of hemorrhoidal disease

Grade of HD	*n*	%	Treatment
Grade I	8144	74	Conservative
Grade II, Grade II with at least 1 grade III, Grade III	2097	19	RBL + IRC
Grade III with at least 1 Grade IV, Grade IV	699	6%	MOH, SH, OH with ligasure

HD: Hemorrhoidal disease; RBL: Rubber band ligation; IRC: Infrared coagulation; MOH: Modified open hemorrhoidectomy; SH: Stapled hemorrhoidectomy; OH: Open hemorrhoidectomy.

in relationship with other treatment options discussed, were discarded for comparison. This gap could not have been levelled out with statistical procedures, even by using statistical bootstrapping techniques.

Analysis of operating times (OT), HT and RTW, compared to all types of procedures, including minimally invasive and invasive ones, is available in Table 4.

A median value of number of cushions per HD grade has been used as comparison for operating times.

As such, the longest operating times recorded for SH, the shortest for RBL + IRC. HT were shortest amongst RBl + IRC, with 1 d, and so were the RTW times, with 1 d. There is a statistical relevant difference of OT, HT and RTW when compared across all types of treatment options.

All surgical procedures (OH, SH, and OH with ligasure) from both clinics, were performed under spinal anesthesia, with Marcaine™ (Bupivacaine, 0.5%, 4 mL). The typical surgical setup included lithotomy position with the operating table 5 degrees tilted in Trendelenburg. For RBL with IRC local topic anesthesia (lidocaine-based) was always used.

The overall complications of the patients that received non-conservative treatment, according to the surgical technique used, are displayed in Table 5. As the aim of the study was not to compare different complication rates between the clinics, these have been reported globally, across all patients in both clinics.

Postoperative complications analysis

The overall complications panel for all 2796 patients treated with different methods, ranging from minimally invasive to invasive solutions, is displayed in Table 6.

Table 4 Comparison between operation times, hostpitalisation times and return to work times across all types of procedures

Criteria	Treatment option	Median (min-max)	*P* value
Operation times (min)	MOH	32.5 (20-45)	0.04
	OH with ligasure	22.5 (10-35)	0.05
	SH	30 (20-40)	0.05
	RBL + IRC	5.5 (2-9)	0.05
Hospitalization times (d)	MOH	4 (2-6)	0.05
	OH with ligasure	2 (1-3)	0.04
	SH	3 (2-4)	0.04
	RBL + IRC	1.5 (1-2)	0.04
Return to work times (d)	MOH	4 (2-6)	0.05
	OH with ligasure	2 (1-3)	0.05
	SH	3 (2-4)	0.05
	RBL + IRC	1 (1-1)	0.05

MOH: Modified open hemorrhoidectomy; OH: Open hemorrhoidectomy; SH: Stapled hemorrhoidectomy; RBL + IRC: Rubber band ligation + infrared coagulation.

Table 5 Complete demographic details of the recorded lot

Criteria	Complication	*n*	%
OH (modified milligan-morgan procedure)	Pain - immediate	664	95
	Pain - delayed	196	28
	Bleeding - immediate postop	10	1.5
	Bleeding - delayed	3	0.5
	Infections of surgical site - perianal abscess	4	0.6
	Anal stricture	10	1.5
Stapled hemorrhoidopexy	Pain	34	4.8
	Bleeding - immediate postop	28	4.0
	Bleeding - delayed		
	Infections of surgical site - perianal abscess	1	0.1
	Anal stricture	6	0.8
	Fecal incontinence	1	0.2
	Urinary retention	2	0.3
Rubber band ligation and infrared coagulation	Pain - immediate	42	2
	Bleeding - immediate postop	40	1.9

OH: Open hemorrhoidectomy.

Pain: In our study, the immediate postoperative pain was present in 90.0% of all patients undergoing different procedures, minimally invasive or otherwise. For the same group, the delayed postoperative pain was present in 28% (783 cases).

For assessing the pain levels, we linked VAS with the need of analgesic medication, reported in mg/24 h, of IV Paracetamol. Results are shown in Table 7.

Reviewing the literature, the physio pathological background for the pain seems to be the reflex contraction of the internal anal sphincter, regarding the surgical trauma, a contraction that outlasts the pain-free interval that spinal anesthesia offers. Therefore, the use of long-lasting local anesthetics (LA),

Table 6 Overall complications in our study

Class of complication	Complication	*n*	%
Pain	Immediate postoperative	2517	90.0
	Delayed postoperative	783	28.0
Bleeding	Immediate postoperative	42	1.5
	Delayed postoperative	28	1.0
Infections of the surgical site	Perianal abscess	14	0.5
	Pelvic abscess	3	0.1
	Fournier`s gangrene	0	0.0
Mechanical complications	Rectal or vaginal perforations	0	0.0
Anal stricture	Immediate postoperative	20	1.0
Fecal incontinence	-	14	0.5
Urinary retention	-	6	0.2

Table 7 Comparison of visual analogue scalescore and the amount of paracetamol IV.

Type of treatment	VAS 4h	VAS 8h	VAS 24h	VAS 7 d	VAS 14 d	VAS 30 d
	Median (min-max)					
MOH	8 (4-12)	7 (3-11)	4 (2-6)	2 (2-2)	0	0
OH with ligasure	6 (3-9)	5 (2-8)	2 (2-2)	2 (1-3)	0	0
SH	3 (3-3)	3 (3-3)	1 (1-1)	1 (1-1)	0	0
RBL + IRC	2 (1-3)	1 (1-1)	0	0	0	0

MOH: Modified open hemorrhoidectomy; OH: Open hemorrhoidectomy; SH: Stapled hemorrhoidectomy; RBL + IRC: Rubber band ligation + infrared coagulation; VAS: Visual analogue scale.

such as Bupivacaine or Tetracaine, is highly recommended by some authors[8-13]. However, our experience differs, as in our study, where surgeries were performed under spinal anesthesia (SA) with Marcaine (0.5% Bupivacaine), since the standard OH can be done in a 30-40 min timeframe, administering a long-lasting LA at the end of the procedure would overlap the pain free interval by almost 90% of the SA, leaving just about 30 minutes, on average, of supplementary protection against pain. As such, our conclusion is that LA should be used only in procedures that extent to the limit of spinal anesthesia. Perhaps the local use of an LA combined with a vasoconstrictor agent, such as 4% Prilocaine and Epinephrine in 1:200.000 ratio, would yield better results in terms of controlling the immediate postoperative pain, but the use of LA and vasoconstrictor agents is not common in general surgery, and we do not recommend it either.

In our study we achieved good postoperative pain control by Paracetamol, IV, after the effects of SA have passed. We never had the need to administer opioid medication and, considering the complications it involves, it should be avoided and kept as a last resort, especially in one-day surgery centers.

Bleeding: Out of all postoperative complications, bleeding is the most feared one by patients and surgeons alike. In our study, the overall immediate postoperative bleeding was recorded in 1.5% of the cases (42 patients) but required no secondary surgery, just monitoring the patient and wound dressing changing. We should mention that we made use of hemostatic cylinder-shaped plugs on a routine basis, in both clinics, if bleeding in the postoperative stage was highly deemed as probable by the surgeon.

Delayed bleeding (in a timeframe of up to 2 wk postoperative) was present in 1% of the cases (28 patients) mostly in patients with LC, and did not require any surgical revision, in contrast with other studies, that indicate as often the need to achieve secondary surgical hemostasis, most likely form an active source, most probable after ligation undoing or a diffuse bleeding that requires hemostatic packings[14].

Comparing bleeding across all types of treatment options, OH had an overall of 2.0% bleeding, with 1.5% immediate and 0.5% delayed, SH had 4.0% immediate bleeding and RBL+IRC had 1.0% (21 patients) immediate bleeding situations.

Bleeding after OH with ligasure was lower, both immediate and delayed, with an overall 1.0% complication rate, proving once again the usefulness of this type of high-energy vessel sealing technique.

Surgical site infections: From the pool of postoperative surgical site infections, in HD treatment, perianal abscesses are amongst the most commonly met, either in conjunction with an inter-sphincter collection or as stand alone. Most of the studies will place them in the range of 1.0% to 8.24% of operated patients and they develop most likely as a result of local determinants, involving a higher bacterial virulence in rectum and anal canal, especially of *Escherichia coli* and gut-specific *Bacteroides* strains, a lack of proper mucosa defending factors such as Immunoglobulin A deficiency, abnormal integrity of the extracellular matrix and epithelial-to-mesenchymal transition or improper bowel preparation prior to surgery[12,15-17].

Our study revealed an overall surgical site infection rate of 0.6% (17 patients), 14 patients with perianal abscesses and 3 with a pelvic abscess, as a result of delayed presentation and late reporting of developing symptoms. All three required reinterventions under SA for surgical drainage and debridement, with a good overall clinical outcome. Severe infectious complications, such as Fournier`s gangrene or even sepsis, have never been recorded in our study, however some publications point out a worrisome percentage of 0.1%[12,18].

Anal stricture: Anal stricture is one of the most feared long-term complications in HD, and every step is required to mitigate this type of complication, as it seriously impacts the quality of life of the patient.

The underlying problem with this type of complication is the strong fibrotic shrinkage phenomenon that occurs after multiple diagonally disposed sites of hemorrhoids have been excised, especially using high energy electrocautery devices[19]. However, the time taken for this complication to fully develop is usually months and even years, and, in rare cases, as much as 20 years. Surgical options to correct this complication range from simple procedures, such as anal pneumatic or instrumental dilatation, to extremely complicated ones, especially if this coexists with other major diagnosis, such as rectal cancer, that requires robotic surgery for an effective low reach[20].

The overall cited incidence is around 1.0% of operated cases[12,15,21]. Our study recorded 0.7% (20 cases) overall rate in the entire lot, most of them form the pool of OH (13 cases) and to a lesser extent form SH (7 cases). RBL and IRC did not determine any anal strictures, as expected. However, the incidence rate of anal stricture was higher than expected when using OH with ligasure, of 8.3%, compared with 1.8% in our modified OH technique or 1.0% for SH.

Fecal incontinence: This type of complication usually appears as a direct damage of the circular muscle fibers of the internal anal sphincter, usually during different types of surgical procedures for perianal fistula repair when it is performed as a stand-alone procedure or as a complementary procedure, such as lateral internal sphincterotomy (LIS) after hemorrhoidectomy with the intention of relieving pain by reducing the postoperative tonicity of the sphincter[22-27]. Damaging the external sphincter muscle fibers is uncommon during these types of procedures. The overall reported incidence of fecal incontinence is in the range of 2.0% to 10.0%, according to most studies[12,15,28,29].

Our study returned a rate of 0.5% of fecal incontinence (14 cases), mainly because we never associate LIS with any of the surgical procedures for HD, open or otherwise. Moreso, a careful evaluation of the internal and external sphincter muscle fibers condition is mandatory in both clinics for preserving the full function of the sphincter. We prefer to deal with the postoperative pain, sometimes triggered by an increased sphincter tonicity, by means of medication, rather than performing LIS. Those 14 cases cases in our study, 11 of them from OH and 3 from SH, perhaps come as a result of hemorrhoids acting as pneumatic barriers against a lower sphincter tonus, prior to surgery, leaving the incontinent sphincter exposed after hemorrhoidectomy. This problem can be successfully avoided by means of intraoperative manometric sphincter tonus determination, a tool that we did not have at our disposal. Again, RBL and IRC did not determine any fecal incontinence.

Urinary retention: The ethiopathogenic explanation for this type of complication would be a combination of a reactive situation to the local trigger of surgical-site pain and as a direct consequence of SA. Many studies underline that SA is a major contributing factor and perhaps resorting to epidural anesthesia can reduce this risk[12,30-33].

Our study recorded just 6 cases (0.2%), all males, of immediate postoperative urinary retention, and this comes in large contrast with different studies that place this type of complication in a range of 0.9% to as much as 30.0%[12,30-32,34].

However, we should mention that all patients in our study, undergoing invasive procedures for HD (OH, SH, OH with ligasure), had a urinary catheter installed after full installment of SA. In our clinics this is the standard procedure to follow, as we believe this offers the best postoperative comfort for the patients, lowers the risk of urinary retention with little to no side-effects. The catheter is held in place for 12 h after surgery and removed prior to the evening sleep. Although urinary infections associated with catheterization are a serious medical problem that may further complicate the postoperative outcome of any patient, including the ones in postoperative HD, the 12h timeframe of the catheterization does not pose such a high risk of infection, provided that all antiseptic procedures have been respected, and

proved successful in eliminating the risk of retention[35-38]. All 6 male patients that had this complication could not have had the catheter installed, due to an ongoing large prostatic adenoma and the other 2 with post *Chlamydia* infection-induced strictures that could not have been resolved either by a Foley probe nor with a Nelaton-type catheter.

Mechanical complications: These mechanical complications stand out as a major type of postoperative development, which includes rectal and/or vaginal perforation, in female patients. Fortunately, rectal perforation is rated at 0.1% of patients and is attributed to SH, mainly, as surgical procedure[12,18,39,40]. Contributing factors are the improper positioning of the stapler during the procedure, preexisting undiagnosed rectal pathology, such as ulcerative recto-colitis (RC) or CD and even vaginal prolapse. Further complications can include pneumoperitoneum or retro-pneumoperitoneum, intra-abdominal bleeding leading, in some of the cases, to severe hypovolemic hemorrhagic shock, and peritonitis[39,41-43].

Our study did not determine any of these types of complications, mainly because we perform colonoscopy on a routine level, so RC or CD is well known in patients scheduled for surgery and we double check the final position of the device prior to firing it.

Complications rates comparison according to procedure types

Cold scalpel OH *vs* high-energy auto-seal hemorrhoidectomy: A direct comparison between OH and CH is not available in our study, as we did not resort to any of the many CH techniques, such as Ferguson`s. However, numerous studies have tried to pinpoint the differences between these procedures, with mixed results. Some major meta-analysis and RTCs clearly demonstrate the superiority of CH, as a surgical option with focus on Ferguson`s technique, in particular, over OH, with Milligan-Morgan procedure as main representative[44-48]. These comparisons were made on all major aspects of HD, such as postoperative pain, risk of postoperative bleeding, time of healing, surgical site infections, long-term anal incontinence, and patient satisfaction. On the other hand, some smaller studies with less than 1000 patients enrolled, show no statistical differences in any key-factors of postoperative evolution of patients with HD, except the time for local healing that seems to be in favor of CH techniques[17,49].

In terms of comparing OH performed with cold-scalpel techniques *vs* hemorrhoidectomy with high-energy auto-seal devices, studies show a better overall response for ligasure, in terms of intraoperative blood loss, immediate pain management, postoperative complications and patient satisfaction[50-54].

In contrast with these reports, our experience with the LigaSure platform shows that anal stricture, as a long-term complication, has higher incidence than OH, even if we apply the ligasure hand piece directly at the base of the hemorrhoidal dilation or after a previous cold scalpel mucous incision and hemorrhoidal pedicle diameter reduction by blunt dissection. By using ligasure we had an anal stricture incidence of 8.3% compared to our modified OH technique, that itself uses standard electrocautery for hemorrhoid stump preparation, indicating that, over long-time, the local perianal tissue response towards ligasure might trigger scar tissue formation with a higher rate, thus leading to a higher rate of anal stricture incidence. For this reason, we stopped using ligasure in any of our procedures, 5 years ago.

Although our modified Milligan-Morgan technique makes use of conventional electrocautery, it cannot be classified as a standard diathermic procedure, since we also secure the hemorrhoidal stump with a transfixing suture. However, several literature reviews that did this type of comparison, between ligasure and standard diathermy, point out a better outcome of ligasure and recommend it for one-day surgery clinics[55-57].

Stapled hemorrhoidopexy *vs* open hemorrhoidectomy: The introduction of SH was a major advancement in surgical options for HD, introducing smaller operating times and less intraoperative bleedings, amongst several other advantages over standard OH. Therefore, the initial clinical response was very good, with many studies and RTCs pointing out less immediate and delayed pain, shorter hospitalization, and better patient work reintegration[58]. However, as complications after this type of procedure can be severe several other studies, RTC and meta-analysis were performed to reevaluate, on the long term, the safety, efficacy, and advantages in terms of cost effectiveness of this method over conventional OH[39,59]. These studies pointed out that recurrence rates, different surgical postoperative complications and overall quality of life after surgery favored OH, with a particular accent on OH being cheaper and with a better cost-to-clinical results ratio[60,61]. Some of the more recent studies suggest that SH is still to be considered as a procedure under evaluation for routine surgical use in the global management of HD, despite its advantages in terms of reduced immediate and delayed postoperative pain, less intraoperative bleeding and shorter hospital stay[61].

Our experience with SH has been a very positive one, with less immediate and delayed postoperative pain (4.8% *vs* 95%), less anal stricture (1.0% *vs* 1.8%) but higher immediate and delayed bleeding (4.0% *vs* 2.0%). Also, from the pool of immediate postoperative complications, SH generated 1 case (0.1%) of perianal abscess that required reintervention, and 0.3% of urinary retention (3 cases) *vs* 0.4% (4 cases). Long term complications recorded 3 cases of fecal incontinence (0.5) but no other severe outcomes, such as Fournier`s gangrene or recto-vaginal perforations.

DG-HAL *vs* OH and SH: DG-HAL was first introduced back in 1995, by Morinaga *et al*[62] and further perfected over the years to provide a safe and modern approach targeted towards one of main pathological triggers of HD: High arterial inflow into hemorrhoidal cushions. Because of its initial excellent results in terms of pain control, intraoperative and postoperative bleeding and anal stricture, many studies tried to assess its effectiveness and efficacy in different degrees of HD[63-67]. For grade II and III it seems to provide promising results, however, in patients with grade III and IV HD we can expect overall postoperative relapses ranging from 24% and up to as much as 67%[68-71]. DG-HAL also has some drawbacks, in terms of high costs and rather long-learning curve needed for a good evaluation of the mucopexy above the dentate line, one of the main reasons attributed to the high recurrence rates [67].

When compared to OH, DG-HAL seems to have better overall results, in terms of lower postoperative pain and less intraoperative bleeding, with the same long-term outcomes, regarding anal stricture in particular, at least for grade II and III HD[12,72,73]. The same study recommends a careful evaluation when it comes to grade IV HD though, indicating fewer effective results. Several meta-analyses comparing DG-HAL with SH draw the same conclusions, that DG-HAL is superior in terms of postoperative pain, immediate or delayed, bleeding and surgical site infection rates[12]. A few studies did not, however, find any significant differences between DG-HAL and SH[74,75].

As previously stated, this technique has not yet been adopted in either of our clinics as a routinely procedure, but the proposal for routine clinical United Statesge is currently under revision in Clinic A. Our study has recorded just 34 cases operated with DG-HAL, for Grade III HD, in the last 4 mo, with very promising results: no intraoperative or immediate postoperative bleeding, less than 5% of patients with a VAS pain score of 3, no fecal incontinence and no local site infections. Also, none of the life-threatening complications were present. However, operating times were 15% longer than a standard OH (for the same number of hemorrhoidal cushions per grade of HD) perhaps this being a result of our limited experience with this technique. Given the very short time that we had with DG-HAL, we can draw no conclusions for any of the long-term complications, such as anal stricture.

RBL + IRC *vs* OH: Many studies point out that OH has overall more complication rates, both immediate and long-term, than RBL with only a few studies point out that the difference, in terms of postoperative complication rates, is not significant[76-80]. However, OH has fewer recurrencies that RBL, being regarded as a one-time surgical solution by many patients, especially those that present several sites of hemorrhoidal cushions. As such, OH can be effective in the range of up to 51% of cases while RBL may need in as much as 34% of the cases, a second intervention[80]. Several studies concur that OH should be reserved for grade III HD and above, as well as for recurrences of HD after previous RBL procedures[77].

From our experience we found that IRC alone has virtually no impact on the evolution of HD, especially in high grades (III or above). For this reason, we always perform IRC as an associated procedure with RBL. Our study recorded immediate postoperative pain in 2.0% cases (42 cases) and immediate bleeding in 1.9% of the cases (40 patients), that needed no surgical hemostasis, however. Also, operating times were much shorter than OH, in terms of effective surgery and especially in time spend in the operating room, since RBL + IRC does not require SA (median 32.5 minutes for OH *vs* median 5.5 minutes for RBL+IRC).

Comparison of preexisting comorbidities and their impact on postoperative evolution of HD

Concomitant colorectal pathology associated with HD: All patients in our study, which received indication for RBL + IRC or surgical treatment (2796 patients), from both clinics, had preoperative total colonoscopy performed, even though the clinical examination had no doubts regarding the positive diagnosis of HD. This comes as a way of screening patients for other coexisting pathologies that might have the same clinical behavior, mainly hemorrhage.

In our study 87 patients (3.1%) had concurrent malignant tumors, mainly located in sigmoid but also in the descendant colon. These patients followed the colorectal cancer protocol and have not been included in this research. Also, our study recorded a total of 995 (35.6%) patients with diverticula (the precise location was not recorded by the study) and 23% polyps (643 patients).

Impact of IBD: Although hemorrhoidal pathology is not the main comorbidity in patients with IBD, large studies show that IBD prevalence in HD can still reach as much as 7%, from which CD and UC are the main representatives[81]. Moreso, there seems to be a difference in newly discovered patients with IBD *vs* patients with chronic evolving pathology, the former displaying a higher overall complication rate than the latter[82]. In general, most studies and meta-analysis agree that both IBDs present some impact on the postoperative course of HD, starting from a general, non-specific level, and down to individual types of complications[12,83]. The overall complication rates can go as high as 40% with immediate postoperative bleeding being the most significant, and local site infections coming in second place with about 12%[84].

Our study recorded 168 patients with IBD form the entire lot of treated patients (2796 patients), with a 1.14 ratio of UC to CD and 6% (42 patients) with IBD from the pool of operated cases (699 cases). The entire distribution of complications and the types of procedures involved in patients with IBD is

displayed in Table 7.

As it can be seen, UC delivered less complications, in both types of treatment option, invasive or conservative procedures.

Impact of AC and AT medication: Numerous studies tried to establish a consensus regarding the definitive risk of actual bleeding in patients with or without ongoing AC or AT medication at the time of HD treatment. However, it seems that we still have contradictive results. Some studies suggest that bleeding was not statistically different for patients with or without AT treatment when undergoing surgical procedures, such as OH or DG-HAL[85,86]. However, larger studies pointed out that delayed bleeding was as high as 4.6% with more than 85% requiring reintervention for secondary hemostasis and even 36% blood transfusion[87,88]. Some of the studies, focusing on both AT and AC medication, came within the same observations, that this class of medication presents significant risks of peri-operative bleeding[88].

Although there is still a strong debate whether the patients undergoing invasive HD surgery should or should not interrupt the administration of AT with several d prior to surgery, our study could not test this theory as all cases selected for invasive procedures have been asked to stop the current AT medication for 3 d prior to surgery, since all of them required spinal anesthesia. Even if novel studies in the field of different types of anesthesia and AT therapy, published by *European Journal of Anesthesiology*, suggest that low dosage of AT, under 200 mg per day and especially in regard to Aspirin, should not be stopped prior to SA as it does not provide a higher risk of peri-procedural bleeding, our anesthesiologist team still follows this protocol[89,90]. Therefore, all 70 cases (2.5% of the treated patients) that developed immediate or delayed bleeding were outside the effects of this type of medication (AT and AC, including NOAC) at the time of surgery.

The same goes for patients with NOACS that underwent conversion protocol to subcutaneous low molecular heparin prior to surgery. For the patients treated with RBL+IRC (2.097) we did not interrupt the ongoing AC or NOAC medication prior to their treatment. From those, 713 patients had AT treatment (34%) based on Clopidogrel (Plavix) and 5% presented significant bleedings (36 patients) that required anal plugging with hemostatic material with 16% insignificant postprocedural bleedings (114 patients) that required simple external compression with wound dressings.

Impact of LC: There are few studies that focus just on LC and how this type of important comorbidity may impact the outcomes of surgery in HD, mainly because these patients will certainly receive major surgical treatment for the underlying pathology – liver transplantation, abdominal tumor resection, vascular procedures for portal vein thrombosis, *etc.* There are few patients requiring dedicated surgery for bleeding hemorrhoidal dilations in this clinical setup.

Even though these studies are scarce, they point out the severity and serious impact of LC over the general complications rates, especially bleeding. However, there is some contradictory data. Some studies would imply that sclerotherapy (SCL) would be the better choice of minimally invasive treatment, after the conservative one failed, against RBL that seems to provide a higher rate of bleeding [91-93]. On the other hand, some other studies could even correlate Child`s score of LC with prognosis and point out that the best course for treatment would be RBL as it provides the lowest recurrence rate for rebleeding, the better patient satisfaction scores and lower need for analgetic medication, compared to SCL[93,94].

DISCUSSION

Even though the Goligher's classification draws much criticism from some important surgical associations (such as Association of Colon and Rectal Surgeons of India), many other major surgical schools still use it for its simplicity and direct connection with the anatomical evidence, therefore our study adhered to this reporting system as well[95]. However, we acknowledge the need for changing the way we classify and report the HD, as this classification does not allow for a standardized surgical approach, does not take into account key factors of HD ethiopathogeny and it is not considering the associated symptomatology nor the dynamic evolution, such as the newly proposed classification system of Rubbini *et al*[96] does**.**

The need for mandatory colonoscopy as a complementary investigation or as a definitive one needed for positive diagnosis of HD is still under debate, especially in private owned clinics where a rapid diagnosis is preferable to shorten the time needed for diagnosis and thus shortening the overall patient hospitalization. However, given that many studies show a high rate of incidental diagnosis of other pathologies, concurrent with HD, such as uncomplicated diverticula, diverticulitis with a silent development polyps and, of course, malignant tumors located above the reach of the standard rectal examination, we believe this type of clinical investigation should be mandatory in all clinics, as a mean of screening[97-105]. In our study, both clinics performed colonoscopy routinely for all grade II and above HD.

Out of all types of hemorrhoidectomies, both clinics in our study rely on a modified Milligan-Morgan, as a surgical solution from the pool of open type procedures. Ferguson, Parks and other closed techniques have never been used. The modification brought to the standard Milligan-Morgan technique brings the advantages of using a standard electrocautery in hemorrhoid surgery, such as faster local coagulation times, better intraoperative bleeding control, but combines them with the advantages of transfixing ligations, such as better control over postoperative bleeding. By bridging these advantages, we believe that we managed to lower the overall complication rates linked with OH techniques.

Our study did not encounter any of the severe local or systemic postoperative complications of HD, such as Fournier`s gangrene or sepsis. Although there is documented evidence that sepsis can have, as a point of origin, a surgical site for hemorrhoidectomy as many of the triggering mechanisms of sepsis are met in the per-operative timeframe, we had no such complications, perhaps due to using the monopolar cautery for the modified Milligan-Morgan procedure, careful hemostasis and use of hemostatic plugs, whenever required and the intraoperative administration of a single antibiotic dose[18,106,107]. However, we cannot substantiate these findings with statistical analysis.

Our study revealed an incidence of 6% of IBDs but we did not record separately the newly diagnosed and chronic patients. We could theorize about the helpful role of chronic consumption of mesalazine (and its derivatives) in these patient`s treatment plan that may offer a better postoperative tissue plasticity and provide a slightly better local regeneration. Perhaps this is the explanation behind the findings of some studies, such as Cracco *et al*[82].

Even though studies that directly compare the efficacy and efficiency of ligasure *vs* harmonic devices are scarce, perhaps because both belong to the same group of high-energy vessel auto-sealing solutions, they still point out that both have similar outcomes in terms of postoperative pain, wound healing time and overall recovery[108]. However, we believe that the slightly lower temperatures of harmonic devices might determine a better long-term tissue response and perhaps a lower anal stricture complication rate[109]. Still, this conclusion is derived from our experience with Harmonic in open or laparoscopic general surgery procedures and has not yet been documented for HD. Since harmonic technology was not available in either of our clinics, LigaSure being the only type of high-energy bipolar device, further studies are required to draw any conclusions from our part, including the need to perform histological determinations to assess the amount of thermal damage of both types of devices.

Even so, we believe that the use of high energy devices should be limited at best or better yet not used at all as they still have a higher anal stricture complication rate in comparison to standard hemorrhoidectomy, even though all other aspects are in favor of vessel sealing platform, such as shorter operating time, and lower intra-operative bleeding[108,110,111].

Some studies show that immediate postoperative pain can be greatly reduced if hemorrhoidectomy, or any invasive procedure for HD, is performed under pudendal nerve block, using long-acting LA such as Bupivacaine or Prilocaine, eliminating the need of a combined SA and LA for the same type of procedures and being superior to just SA[112,113]. However, in our study, where all patients had SA with Bupivacaine, the immediate postoperative pain was lower than comparative studies, without the need of supplementing with any other LA, perhaps because OH or SH fit well within the 180 min SA duration, with operating times of just 30-40 min. This provides a long-time reserve until SA wears out, allowing for local inflammation to resorb and thus leading to lower levels of immediate pain.

We successfully managed to avoid urinary retention by routinely deploying urinary catheters in all patients undergoing invasive procedures, such as OH, SH or OH with ligasure under SA. We did not record any urinary infectious complications in any of the patients with urinary catheters. We believe that, if proper antiseptic procedures are respected, and the probe does not stay in place for more than 12 h, the risk is minimally, as the data in our study shows. Also, the routine IV administration of ceftriaxone (Cefort™), a 3rd generation cephalosporin, single intraoperative dose of 2 g, might have helped achieving these results, even though this class of antibiotic is not the first line of choice in urinary tract infections.

Limitations of the current study: Although careful intraoperative and postoperative evaluations were performed, none of our patients received pre- and postoperative manometric sphincter determinations to assess the level of remnant tonicity in comparison with the preoperative one, as neither of the two clinics have access to such investigation. This would, perhaps, have served better the patients with long term complications, such as anal stricture, allowing us to have a superior control over the rates for this type of postoperative complication.

Although human immunodeficiency virus (HIV)-induced immunodeficiency is a documented risk factor that increases the chances of anorectal infections and may delay surgical site regeneration after coloproctological procedures, no matter the type, whether classic hemorrhoidectomy sclerotherapy or RBL, this study did not focus on this particular comorbidity, as patients are not routinely checked for HIV infections and many are reluctant to declare such pathology, during initial evaluation[114-116].

CONCLUSION

Treatment of hemorrhoidal disease should benefit from a very tailored treatment plan, after a careful grade assessment of the patient. As such, we think grade I HD benefits most after conservative, medication-based and dietary treatments; an all-grade II HD patients or patients with a mixture of grade II and grade III HD or patients with all-grade III HD will benefit best from rubber band ligation with infrared coagulation as this provides the best balance in terms of safety, cost effectiveness and low complication rates. Patients with at least one hemorrhoidal cushion in grade IV, disregarding the predominant number of cushions with lower grades, should automatically benefit from either open hemorrhoidectomy or stapled hemorrhoidopexy, as neither RBL with IRC nor ligasure could provide the same overall satisfactory results. We propose our modified Milligan Morgan OH technique that has many advantages, even though marginal, over the standard OH because it provides less intraoperative and postoperative bleeding, reduces the risk of reinterventions for bleeding control and has an overall lesser chance of developing anal stricture, even though it induces higher immediate and delayed postoperative pain levels compared to SH. We believe stapled hemorrhoidopexy should be carefully considered carefully as it can be responsible for severe postoperative complications, especially in patients with IBD, such as CD.

Open hemorrhoidectomy by high-energy vessel-sealing platforms, such as ligasure, may cause significant anal stricture and should be avoided, even though they can provide a better intraoperative bleeding control and overall shorter operating times.

We did not find any evidence suggesting the need of a supplementary local anesthetic in the perianal area, in patients operated with spinal anesthesia; immediate postoperative pain control in these patients could be successfully achieved with standard IV analgesics, such as Paracetamol.

Stopping the antithrombotic medication, especially Clopidogrel, is not mandatory from a surgical point of view, but advisable, especially in patients with a predominant grade IV hemorrhoidal disease as it can provide better intraoperative bleeding control and reduces the chances of reintervention.

Routinely placement of a urinary catheter for 12 h postoperative will significantly reduce the chances of urinary retention without significantly increasing urinary infection rate.

Using anal plugs, either in the form of simple gauze, for 12 h postoperative, or as a rectal expandable hemostatic foam will significantly reduce the immediate postoperative bleeding without with little to no discomfort for the patient, if correctly applied.

ARTICLE HIGHLIGHTS

Research background

For many years hemorrhoidal disease (HD) has been perceived by society as a low-severity pathology, this perception being adopted even by physicians, albeit not gastroenterologists or surgeons. However, if we add the very high prevalence rate, of more than 10% of the adult population, the overall long length of conservative medication-based therapy and the severity of complications after surgery, it becomes clear that this is truly a disease that should change the perspective.

Research motivation

To provide clinicians, both gastroenterologist and colorectal surgeons, the proper tools to better outlay the treatment options factoring in patients' comorbidities, chronic medication and the severity of hemorrhoidal disease.

Research objectives

To compare the overall clinical results of different surgical techniques on patients with grade II and above of HD and different comorbidities with documented impact in the development and evolution of HD.

Research methods

We developed a multicentric retrospective study that covers 10 years of treating patients with hemorrhoidal pathology, in two major clinics, a private-based medical facility and a state-owned hospital. Between January 2011 and December 2021, a total of 10.940 patients have been enrolled and treated for hemorrhoidal disease, in various stages and with different methods, ranging from medical options to surgical ones. The study also recorded full demographic details, classification of hemorrhoidal pathology before surgery as well as a comprehensive comorbidities panel, including inflammatory bowel disease, anticoagulant medication, and liver cirrhosis, all medical conditions with documented impact with impact on HD. Other important details such as length (in minutes) of surgical procedure, duration of hospitalization, return to work time, type of complications developed and their time of onset, in respect to the initial procedure have been recorded. Regarding the surgical procedures we noted open hemorrhoidectomy (OH) with a modified OH, stapled hemorrhoidopexy (SH) and

rubber band ligation (RBL) with infrared coagulation (IRC). For comparison purposes we constasted our data with the ones in international literature by performing a review consisting in a custom interrogation of PubMed and PubMed Central for the terms "hemorrhoid" and "postoperative" and "complications", for the past 20 years (2002-2022) and selecting clinical trials, meta-analysis, randomized control trials, reviews, and systematic reviews as scientific sources, resulting in a list of 1263 articles.

Research results

Our study recorded a total of 10.940 patients diagnosed with HD, 8144 patients (74%) receiving conservative, medication-based treatment and 2796 being treated with minimally invasive procedures (2097 patients) or with invasive techniques (699 patients). Regarding the treatment, patients with grade I pathology (74%) received conservative therapy. Non-surgical treatment with RBL and IRC was applied to patients with grade II HD and all patients with grade II that also had at least one grade III hemorrhoidal dilation plus all grade III (19%). Surgical treatment consisting of OH, SH or OH with ligasure, 6% of cases, was reserved for patients with grade III HD that also had at least one grade IV dilation, and patients with fully grade IV pathology.

Research conclusions

We strongly believe that a complete and efficient treatment of hemorrhoidal disease should be a highly tailored one, based on a very good clinical assessment of the patient. Reviewing our lot of patients and procedures, we think that open hemorrhoidectomy by high-energy vessel-sealing platforms may induce significant anal stricture and should be avoided, even though they provide a better intraoperative bleeding control and overall shorter operating times. As demonstrated by clinical data obtained in this study, we believe that our modified Milligan Morgan OH technique has many advantages, even though arguably marginal, over the standard OH, but more than enough to possibly make it a routine procedure in patients with grade IV HD.

Research perspectives

Further study that includes patients with HD and HIV-induced immunodeficiency is in order, since this is a documented risk factor that increases the chances of anorectal infections therefore the postoperative development can be very unpredictable and may render different results then the ones in our study. Also, a full manometric evaluation, both prior and in the postoperative state can give us a more detailed information regarding the actual impact of different surgical techniques and tools, especially in regard to high-energy platforms.

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FOOTNOTES

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ORIGINAL ARTICLE

Observational Study

Tear inflammation related indexes after cataract surgery in elderly patients with type 2 diabetes mellitus

Jun Lv, Cheng-Jian Cao, Wei Li, Shuang-Le Li, Jun Zheng, Xiu-Li Yang

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Abstract

BACKGROUND

Quantitative studies on the changes in inflammation-related content in tears, especially the effect of diabetes, are lacking. In this study, we measured the preoperative and postoperative tear inflammatory mediator levels in cataract patients, focusing on the expression of inflammatory factors in postoperative cataracts in the diabetic, and investigated the effect of drugs on the control of postoperative inflammation.

AIM

To study the expression of inflammatory factors in elderly people with type 2 diabetes after cataract surgery.

METHODS

Patients with a mean age of 70.3 ± 6.3 years were divided into group A (composed of elderly patients with cataracts and type 2 diabetes, n = 20 eyes) and group B (patients with age-related cataract, n = 20 eyes). Their tears were collected before each operation and on days 1 and 3, and weeks 1, 2, 3, and 4 post-surgery. Saline (150 μL) was dropped into the conjunctival sac of the surgical eye, followed by oculogyration in four directions. The fluid in the conjunctival sac was extracted using a sterile syringe and stored in Eppendorf tubes at -80 °C until measurement. The expression levels of matrix metalloproteinase-2 (MMP-2), MMP-9, tissue inhibitor of metalloproteinase-1 (TIMP-1), TIMP-2, interleukin-6 (IL-6), and IL-20

in tear fluid were measured using enzyme-linked immunosorbent assays.

RESULTS

The postoperative expression levels of MMP-2, MMP-9, TIMP-2, IL-6, and IL-20 in group A were significantly higher than those in group B, whereas the concentration of TIMP-1 in group A remained lower than that in group B. The levels of MMP-2 and IL-6 in both groups continuously increased until the peak in the first postoperative week, and then gradually decreased over the next three weeks. Ultimately, MMP-2 declined to a lower level than that preoperatively at week 4, but IL-6 decreased to the same level as that preoperatively. The level of MMP-9 peaked in the first two weeks postoperative and then returned to the same level as 1-day post-operation. The concentration of TIMP-1 post-operation remained constant at a lower level than before surgery, and TIMP-2 Levels remained stable in both groups. IL-20 content started to increase in the third week after surgery.

CONCLUSION

Inflammatory factor levels in tears fluctuated before and post-operation, which indicated more severe postoperative inflammation in the first two weeks.

Key Words: Type 2 diabetes mellitus; Elderly patients; Cataract surgery; Tear inflammation-related indicators; Temporal changes; Prognosis

Core Tip: In this study, we compared the expression of inflammatory factors in postoperative tears of cataract patients and found that postoperative inflammation was more severe in elderly patients with cataract combined with type 2 diabetes; moreover, the level of postoperative inflammatory factors fluctuated greatly, and the inflammation was more severe in the first two weeks after surgery.

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INTRODUCTION

Cataracts are the main cause of blindness and affect millions of people worldwide[1]. Diabetes is one of the most prevalent chronic diseases in the world. Patients with type 2 diabetes have a higher risk of cataracts than those without diabetes and require surgery more urgently[2]. Cataract patients with diabetes are also at a higher risk of delayed incisional healing and postoperative complications, such as dry eye, corneal epithelial defects or erosions, persistent inflammatory reactions, and infections[3]. Currently, China is rapidly becoming an aging society, with an increasing proportion of the aged population. Changes in tear composition in elderly patients resulting from loss of the meibomian gland gradually aggravate with age. Additionally, abnormal diabetes-induced variations in tear components might cause postoperative inflammatory reactions in patients with type 2 diabetes[4]. Xerophthalmia was observed significantly more frequently in diabetic patients than in non-diabetics 7 d after phacoemulsification[5]. Another retrospective clinical study confirmed that the risk of complications in patients with diabetes was highest in the first 2 wk after cataract surgery[6].

The development of postoperative inflammation may be significantly affected by these inflammation-related mediators, but quantitative studies on inflammatory-related content changes in tears, particularly the effect of diabetes mellitus, are still lacking. This study focused on the postoperative expression of inflammatory factors in elderly diabetic cataracts to discuss the effects of drugs on the control of postoperative inflammation.

MATERIALS AND METHODS

Patients

Patients diagnosed with age-related cataracts and treated with cataract surgery in our hospital between December 2021 and January 2022 were divided into group A (cataract with combined type 2 diabetes

mellitus, n = 20 eyes) and Group B (elderly patients with cataracts but no diabetes, n = 20 eyes).

The inclusion criteria were as follows: patients with cataract with or without a confirmed history of type 2 diabetes mellitus, eligibility for geriatric cataract surgery, clear state of consciousness, and ability to cooperate with relevant examinations.

Exclusion criteria: Patients with previous/current ocular/systemic inflammation, fever, immunological diseases, history of ocular surgery or trauma, intraoperative complications, or inability to cooperate with examinations.

General clinical parameters, such as age, sex, body temperature, height, and weight, and detailed medical history were acquired, measured, and recorded. Hemanalysis and measurement of indicators were performed for all patients, including blood glucose, triglycerides (TG), total cholesterol (TC), glycated hemoglobin (HbA1c), glycated albumin (GA), tear matrix metalloproteinase-2 (MMP-2), MMP-9, tissue inhibitor of metalloproteinase-1 (TIMP-1), TIMP-2, interleukin-6 (IL-6), and IL-20. All patients underwent ophthalmic observations and examinations, including visual acuity (before and postoperative, categorized as ≤ 0.3, 0.3-0.6, and ≥ 0.6), intraocular pressure, slit lamp examination, fundus state, cataract-related preoperative examinations, ocular-surface states, healing and inflammatory states of corneal incision.

Tears collection and measurement

Tears were collected before surgery and on days 1 and 3 and weeks 1, 2, 3, and 4 post-operation. Saline (150 μL) was dropped into the conjunctival sac of the surgical eye, followed by oculogyration in four directions. The fluid in the conjunctival sac was extracted using a sterile syringe and stored in Eppendorf tubes at -80 °C until measurement. The concentrations of MMP-2, MMP-9, TIMP-1, TIMP-2, IL-6, and IL-20 in the tear fluid were measured using enzyme-linked immunosorbent assay.

Surgical procedure

All patients were administered pranoprofen eye drops 3 times/d and levofloxacin eye drops 3 times/d, three days before surgery. All procedures were performed by the same surgeon. Mydriasis was induced with compound tropicamide 30 min before surgery and surface anesthesia with oxybuprocaine hydrochloride drops before surgery. A main incision was made on the temporal side of the transparent cornea, and a secondary incision was made on the inferior temporal (left eye) or superior temporal (right eye) side of the transparent cornea. Continuous circular capsulorhexis was performed through the injection of viscoelastic agents, the nucleus was emulsified after hydro-dissection and hydro-delineation, followed by aspiration of the cortex, and the intraocular lens was implanted into the polished capsular bag. Surgery was completed after irrigation of the anterior chamber, aspiration of viscoelastic agents, and closure of the conjunctiva with solution. After surgery, all patients were administered tobramycin and dexamethasone eye drops three times/d for one month, pranoprofen eye drops three times/d for two weeks, and levofloxacin eye drops three times/d for two weeks.

Statistical analysis

Differences in inflammatory factor expression (indicated as mean and standard deviation) between diabetic and non-diabetic elderly patients with cataract were determined by performing repeated-measures and Analysis of Variance using SPSS 26.0. Differences in age, intraocular pressure (IOP), HbA1c, GA, TG, and TC between the two groups were verified using Student's test in SPSS 26.0. Differences in sex between the two groups were determined using the χ^2 test. Statistical significance was set at $P < 0.05$.

RESULTS

Comparison of general information

A comparison was performed with 19 eyes of 19 males (47.5%) and 21 eyes of 21 females (52.5%), whose mean age was (70.3 ± 6.3) years, and the mean disease course duration of diabetes in group A was (6.8 ± 2.2) years. Patients were further grouped based on their preoperative visual acuity as ≤ 0.1, 0.1-0.3, and ≥ 0.3. The composition of sex and age, visual acuity, IOP, TG, and TC between the groups was not significantly different, while significant differences were detected in HbA1c and GA (Table 1).

Changes in the expression levels of MMP-2 and MMP-9 in tear fluid at each time point in the two groups

The level of MMP-2 in both groups continuously increased until it peaked in the first week postoperatively and then gradually decreased over the next three weeks, ultimately declining to a level lower than the preoperative level at week 4. The level of MMP-9 peaked in the first two weeks postoperative and then returned to the same level as 1-day post-operation. The expression levels of MMP-2 and MMP-9 in group A were significantly higher than those in group B at all time points (Table 2, Figure 1A and B; $P < 0.001$).

Table 1 Comparison of general information between two groups of patients

Groups	Age[1] (yr)	Gender[2] (M/F)	Visual acuity (BCVA)[3]			Intraocular pressure[1] (mmHg)	HbA1c[1] (%)	GA[1] (%)	TG[1] (mmol/L)	TC[1] (mmol/L)
			≤ 0.1	0.1-0.3	≥ 0.3					
Group A	69.3 ± 6.6	9/11	9	8	3	15.3 ± 2.28	8.2 ± 0.6	25.1 ± 4.8	2.0 ± 0.3	5.7 ± 0.4
Group B	71.0 ± 5.0	10/10	8	10	2	15.8 ± 2.76	5.4 ± 0.1	14.0 ± 1.5	1.7 ± 0.3	5.6 ± 0.4
χ^2/F value	1.196	0.100		0.481		0.225	8.197	8.700	0.238	0.749
P value	0.557	0.752		0.829		0.575	0.002	0.020	0.458	0.142

[1]The use of two independent samples *t*-test.
[2]The use of the χ^2 test.
[3]The use of Pearson's χ^2 test.
HbA1c: glycated hemoglobin; GA: glycated albumin; TG: triglycerides; TC: total cholesterol.

Table 2 Comparison of matrix metalloproteinase-2 and matrix metalloproteinase-9 levels in the tears of two groups at different time points

Time	MMP-2 (ng/mL)				MMP-9 (ng/mL)			
	Group A	Group B	*t* value	*P* value	Group A	Group B	*t* value	*P* value
Preoperative	11.13 ± 0.56	8.83 ± 0.88	11.65	0.000	36.07 ± 1.82	25.55 ± 1.74	13.22	0.000
1 d	10.71 ± 0.68	8.07 ± 0.68	10.54	0.000	42.90 ± 1.82	32.69 ± 2.33	10.96	0.000
3 d	13.53 ± 0.79	10.42 ± 0.96	11.06	0.000	43.37 ± 1.33	32.80 ± 1.02	18.09	0.000
1 wk	14.45 ± 0.9	10.54 ± 0.94	8.22	0.000	56.25 ± 1.96	43.02 ± 1.45	20.45	0.000
2 wk	13.17 ± 0.93	9.43 ± 0.49	12.29	0.000	72.78 ± 1.66	51.99 ± 1.71	41.48	0.000
3 wk	11.37 ± 0.40	9.15 ± 0.60	9.99	0.000	43.81 ± 2.68	32.55 ± 1.3	14.70	0.000
4 wk	8.77 ± 0.83	7.62 ± 0.84	2.63	0.017	44.41 ± 3.15	31.97 ± 1.58	13.79	0.000

MMP: Matrix metalloproteinase.

Changes in the expression levels of TIMP-1 and TIMP-2 in tear fluid at each time point in the two groups

After a decline in the first two postoperative weeks and an increase from the third week, the concentration of TIMP-1 in group A was still lower than that before surgery at four weeks post-operation. The expression level of TIMP-1 in group A was lower than that in group B (Figure 1C, $P < 0.05$). The level of tear TIMP-2 in group A was higher than that in group B before and after operation (Table 3, Figure 1D; $P < 0.01$).

Changes in IL-6 and IL-20 expression levels in tear fluid at each time point in both groups

After surgery, IL-6 Levels in both groups increased in the first week, but remained at a higher level in group A than in group B (Figure 1E, $P < 0.001$). Similar trends in IL-20 Levels were observed in the two groups, which were also higher in group A than in group B ($P < 0.05$). Its concentration remained constant before the third week after operation, surged to a peak in the third week post-operation, and then started to slump in the fourth week (Table 4, Figure 1F).

DISCUSSION

Hyperglycemia contributes to impaired corneal sensitivity, reduces nerve fiber density, and delays epithelial wound healing. Due to reduced corneal sensitivity, reflex-induced tear secretion decreases together with the blink rate in diabetic patients, which ultimately leads to increased tear evaporation[7]. Corneal incision accompanied by nerve amputation and microscopic light illumination in cataract

Table 3 Comparison of tissue inhibitor of metalloproteinase-1 and tissue inhibitor of metalloproteinase-2 levels in the tears of two groups of patients at different time points

Time	TIMP-1 (ng/mL)				TIMP-2 (ng/mL)			
	Group A	Group B	*t* value	*P* value	Group A	Group B	*t* value	*P* value
Preoperative	5.24 ± 0.13	5.77 ± 0.10	2.34	0.032	4.28 ± 0.15	3.33 ± 0.28	6.13	0.004
1 d	5.25 ± 0.15	5.76 ± 0.12	2.06	0.028	4.22 ± 0.18	3.58 ± 0.34	6.01	0.003
3 d	5.23 ± 0.14	4.89 ± 0.11	2.83	0.027	4.19 ± 0.13	3.71 ± 0.2	5.41	0.007
1 wk	4.57 ± 0.15	4.61 ± 0.23	0.45	0.060	4.28 ± 0.13	3.44 ± 0.36	5.08	0.006
2 wk	4.20 ± 0.13	5.51 ± 0.15	2.75	0.021	4.23 ± 0.18	3.51 ± 0.31	6.51	0.002
3 wk	4.71 ± 0.18	5.50 ± 0.14	5.75	0.005	4.29 ± 0.16	3.50 ± 0.35	6.60	0.004
4 wk	4.70 ± 0.17	5.77 ± 0.13	7.34	0.003	4.19 ± 0.16	3.50 ± 0.37	6.64	0.003

TIMP: Tissue inhibitor of metalloproteinase.

Table 4 Comparison of interleukin-6 and interleukin-20 levels in the tears of two groups of patients at different time points

Time	IL-6 (pg/mL)				IL-20 (pg/mL)			
	Group A	Group B	*t* value	*P* value	Group A	Group B	*t* value	*P* value
Preoperative	42.84 ± 1.49	29.89 ± 1.09	22.33	0.000	579.90 ± 13.89	533.15 ± 10.9	2.78	0.021
1 d	42.77 ± 1.18	30.17 ± 1.11	24.65	0.000	576.82 ± 10.67	535.13 ± 16.38	2.39	0.024
3 d	48.11 ± 2.01	33.79 ± 1.08	19.90	0.000	587.52 ± 7.62	534.28 ± 17.92	2.91	0.037
1 wk	53.85 ± 1.24	42.97 ± 0.52	25.76	0.000	578.75 ± 13.9	539.97 ± 11.95	2.50	0.038
2 wk	49.58 ± 2.02	37.82 ± 1.55	14.63	0.000	579.08 ± 11.15	534.64 ± 13.27	2.67	0.035
3 wk	42.64 ± 1.43	31.44 ± 1.57	16.73	0.000	702.67 ± 35.3	679.85 ± 26.2	2.62	0.032
4 wk	35.82 ± 1.14	29.79 ± 0.81	13.70	0.000	619.55 ± 60.04	570.05 ± 15.94	2.43	0.036

IL: Interleukin.

surgeries, use of anesthetics, mydriatic drops, and postoperative antibiotics and hormones increases the risk of postoperative complications in diabetic patients. In summary, patients with type-2-diabetes with cataracts are at a higher risk of postoperative complications and have more difficulty in epithelial wound healing than cataracts in patients with normal blood glucose levels, which suggests that more attention should be paid to their treatment.

MMPs are a highly conserved family of proteinases that can degrade various extracellular matrix components[8]. The expression levels of MMPs are extremely low under normal physiological conditions and can be significantly upregulated by inflammatory factors, growth factors, and pathological conditions such as high glucose and oxidative stress. TIMPs are active in many tissues and body fluids as endogenous inhibitors of MMPs[9]. It was confirmed both *in vitro* and *in vivo* that upregulated expression levels of MMP-2 and MMP-9 in wound healing of high glucose cultured corneal epithelial cells and corneal epithelial cells from diabetic rats can lead to xerophthalmia, defects, and erosions of corneal epithelial and ocular inflammation[10]. Increased MMP-9 expression in ocular tissues has also been observed in recurrent corneal erosion, skin ulcers, and diabetic retinopathy[11]. Tears containing levels of MMP-2, MMP-9, and TIMP-2 before and post-operation, were estimated to be higher in patients with diabetes than in elderly patients with cataracts but no diabetes. It is thought to be a response to the stimulation of the ocular surface by long-term high blood glucose concentrations and chronic inflammation. In addition, the gradual increase in MMP-2/9 Levels in the first two postoperative weeks suggested that severe inflammatory responses occurred in the first two weeks post cataract surgery. TIMP-1 expression was suppressed after surgery in both groups and was more significant in group A. This suppression works in concert with the upregulated expression of MMPs and ultimately causes severe inflammation in patients with diabetes.

IL-6 is a pleiotropic cytokine that affects various cell types, including pro-inflammatory and anti-inflammatory cytokines[12]. Dysregulation of IL-6 signaling is associated with the pathogenesis of several autoimmune and inflammatory diseases, including type 2 diabetes[13]. The causality between

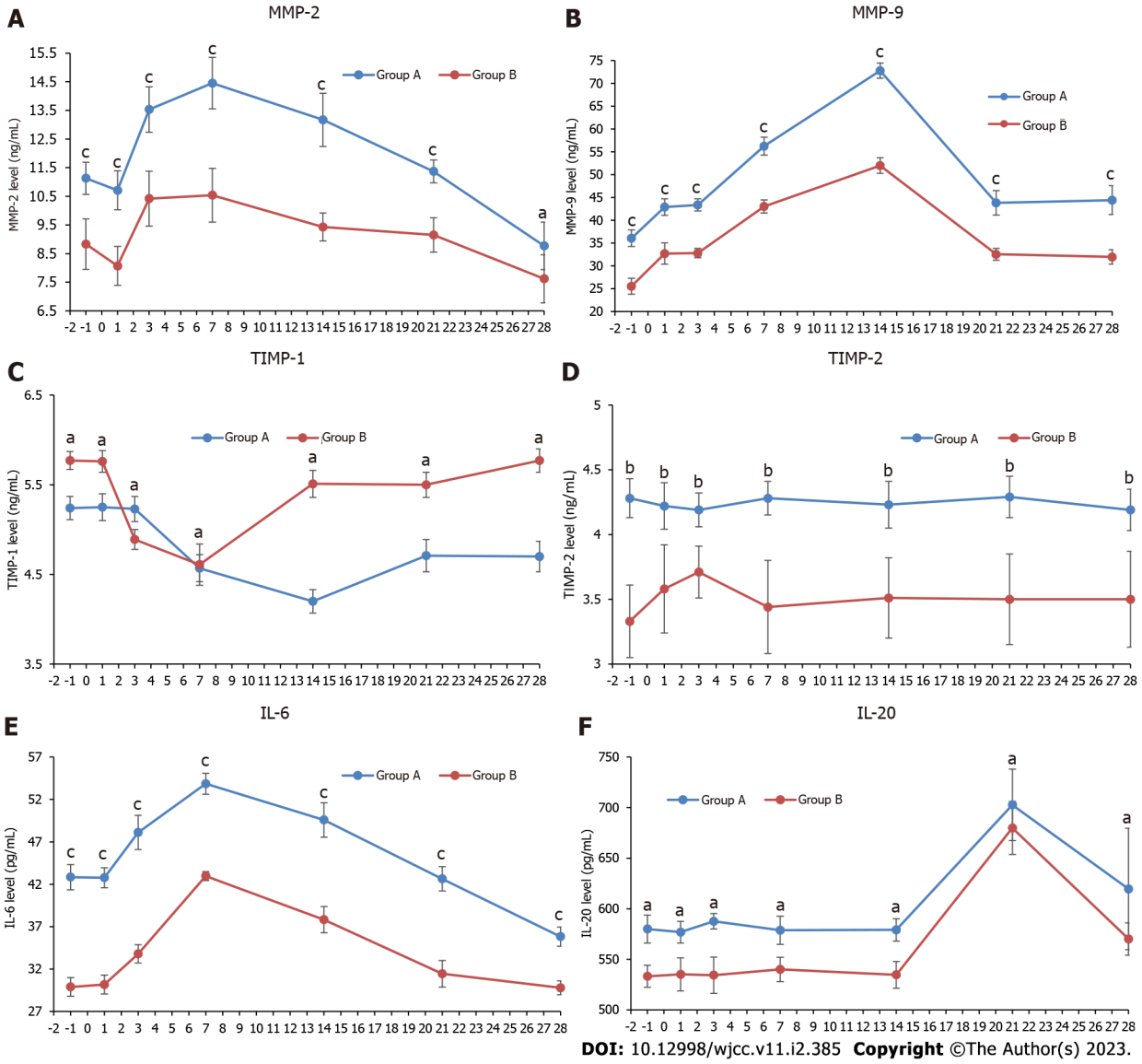

Figure 1 Changes of some indicators' levels in tears before and after surgery in both groups. A: Matrix metalloproteinase-2 (MMP-2); B: MMP-9; C: Tissue inhibitor of metalloproteinase-1 (TIMP-1); D: TIMP-2; E: Interleukin-6 (IL-6); F: IL-20. $^{a}P < 0.05$, $^{b}P < 0.01$, $^{c}P < 0.001$. MMP: Matrix metalloproteinase; TIMP: Tissue inhibitor of metalloproteinase; IL: Interleukin.

chronic low-grade inflammation, indicated by elevated circulating levels of inflammatory cytokines (*e.g.*, IL-6), and the pathogenesis of type 2 diabetes has been progressively verified[14]. Previous studies have shown that during trauma, many inflammatory cells accumulate and release early inflammatory mediators, mainly tumor necrosis factors-α and IL-6, which initiate a systemic inflammatory response and promote the expression of MMP-2, the overexpression of which is responsible for the disease. In corneal keratopathy, IL-6-mediated MMP-2 expression results in continuous tissue necrosis followed by degradation[15].

The interaction between IL-20 and its receptor may have pro-inflammatory, angiogenic, and chemo-attractive effects in chronic inflammatory diseases, especially atherosclerosis and rheumatoid arthritis. This may also have a certain degree of impact on type 2 diabetes. We also detected the expression of IL-20 and related receptors in corneal epithelial cells, dendritic cells, and monocytes of wild-type mice. By promoting the aggregation and activation of T-cells in the injured cornea, IL-20 exerts anti-inflammatory effects without increasing neutrophil chemotaxis or promoting corneal epithelialization and wound healing[16]. This process of corneal re-epithelialization can be inhibited by the absence of neutrophils or T cells. In this study, IL-6 Levels gradually increased to a peak on days 1 and 3; and on week 1 post-operation, and then gradually decreased at weeks 2, 3, and 4 post-operation. This might be related to the gradual aggravation of early inflammation, which could induce the expression of IL-6 to further promote anti-inflammatory effects after cataract surgery. The increase in IL-20 in the third week after cataract surgery might be caused by the decreased release of inflammatory factors in the third week after cataract surgery, which could promote IL-20 expression and further contribute to corneal wound healing.

In this study, as there was a trend of correlated changes in postoperative inflammatory factor expression when the same ophthalmic medication was applied pre and postoperatively to the eyes of both groups, it was speculated that the application of anti-inflammatory and infection-preventive ophthalmic drugs before and after surgery had an effect on postoperative healing. Meanwhile, both the pre and postoperative levels of relevant inflammatory factors were higher in the test group than in the control group, indicating that the postoperative inflammatory response was higher in the test group based on the application of the same dosages of ophthalmic drugs. Therefore, it was considered clinically that within one week after cataract surgery, the frequency and duration of relevant ophthalmic drugs could be increased to reduce the postoperative inflammatory response in patients with combined diabetes and cataracts. Another study found that the use of ultrasound emulsification combined with IOL implantation based on routine glycemic control, IOP control, and anti-inflammation in patients with cataracts combined with diabetes, reduced the levels of inflammatory factors in the atrial fluid and oxidative stress indicators in such patients[17].

Our study has several limitations. First, it was a small sample; second, there was a lack of information about the patients' blood glucose levels and the duration of their disease, and some patients may have been undiagnosed or were untreated for diabetes before surgery; third, the number of preoperative tears and tear volume in patients was inadequate.

CONCLUSION

Comparison between inflammatory indices at different time points before and after surgery revealed more severe postoperative inflammation in patients with Type 2 diabetes with cataracts than in elderly patients with cataracts but without diabetes. Postoperative levels of inflammatory factors in tears were fluid, particularly compared to levels before-the operation. The expression of most inflammatory factors peaked in the first two weeks after surgery, when patients were considered most vulnerable to inflammatory complications. Therefore, the increased use of anti-inflammatory drugs in the first two postoperative weeks was proposed based on our observations.

ARTICLE HIGHLIGHTS

Research background

Quantitative studies on the changes in inflammation-related content in tears, especially the effect of diabetes, are lacking. In this study, we measured the preoperative and postoperative tear inflammatory mediator levels in cataract patients, focusing on the expression of inflammatory factors in postoperative diabetic cataracts in the elderly, and investigated the effect of drugs on the control of postoperative inflammation.

Research motivation

Postoperative inflammation is more severe in diabetic patients with cataracts than in elderly cataract patients who are not diabetic, and the level of inflammatory factors in the postoperative tears is also higher in the former. Therefore, this strengthened the recommendation for the use of anti-inflammatory drugs in the first two postoperative weeks, that was proposed based on our observations.

Research objectives

This study studies the expression of inflammatory factors in elderly people with type 2 diabetes after cataract surgery. This may provide a basis for the timing and duration of anti-inflammatory medication use in patients undergoing cataract surgery.

Research methods

This study was an observational study. The patients were divided into two groups. Group A (patients with cataracts with combined type 2 diabetes) and group B (patients with cataracts without combined type 2 diabetes). Their tears were collected before each operation and on days 1 and 3 and weeks 1, 2, 3, and 4 post-surgery, and an enzyme-linked immunosorbent assay was used to detect the level of inflammatory mediators in tear fluid.

Research results

The expression levels of matrix metalloproteinase-2 (MMP-2), MMP-9, tissue inhibitor of metalloproteinase-2 (TIMP-2), interleukin-6 (IL-6), and IL-20 in group A were significantly higher than those in group B after surgery, whereas the expression level of TIMP-1 in group A was always lower than that in group B.

Research conclusions

Postoperative tear inflammation is more severe in cataract patients with diabetes than in elderly patients. Inflammatory factor levels in tears fluctuated before and post-operation, which indicated more severe postoperative inflammation in the first two weeks.

Research perspectives

Future studies should expand the sample size, standardize inclusion criteria for cataract patients with or without type 2 diabetes, measure their blood glucose levels before surgery, and investigate other disease characteristics to reduce confounding factors and increase the number of preoperative tear collections and tear volumes for patients.

FOOTNOTES

Author contributions: Li SL was the guarantor and proposed the research topics; Lv J designed the research protocols and wrote the manuscript; Cao CJ and Zheng J participated in the analysis and interpretation of the data; Li W revised the major elements of the manuscript; Yang XL participated in data collection; all authors reviewed and approved the final version to be published.

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CASE REPORT

Management of a rare giant cell tumor of the distal fibula: A case report

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Abstract

BACKGROUND

Aggressive giant cell tumor of the distal fibula is so rare that no consensus on a surgical strategy has been reached. Thus, an appropriate treatment strategy is still important to discuss.

CASE SUMMARY

A 61-year-old man who had been experiencing progressive swelling of the left lateral malleolus accompanied by pain for half a year was presented at our hospital. He had never been treated prior to coming to our hospital. Preoperative imaging revealed a 10 cm × 6 cm mass located in the body of the distal fibula. Pathological biopsies confirmed it was a giant cell tumor. Preoperative examination revealed he had dilated cardiomyopathy with class 3 cardiac function. The cardiologist and anesthesiologist determined that he could tolerate the operation, but the operation should be as short and minimally invasive as possible. With the patient's consent, we performed a tibiotalar fusion and followed up with him for 2 years, finding no recurrence and a satisfactory recovery.

CONCLUSION

Tibial talus fusion is an effective method for the treatment of distal fibula tumors.

Key Words: Giant cell tumor; Distal fibula; Tibiotalus fusion; Ankle function; Case report

Core Tip: Giant cell tumor of the distal fibula is rare, and tibiotalus fusion has not been reported in the treatment of Campanacci III giant cell tumor of the fibula. In this study, the tibial talus joint was fused with three screws, and the follow-up for 2 years showed satisfactory efficacy and no recurrence.

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INTRODUCTION

Giant cell tumor of bone (GCTB) is an intermediate locally aggressive tumor comprised of osteoclast-like multinuclear cells and hyperplastic mononuclear interstitial cells[1,2]. There is a risk of malignant transformation, although it is only described in rare cases[3,4]. GCTB is a rare primary tumor and accounts for 4%-5% of primary bone tumors[5]. It usually involves the metaphyseal-epiphyseal region of the long bones, with about 50% of tumors occurring in the distal femur, proximal tibia, and distal radius[1,5]. The other less common sites are the distal tibia, proximal humerus, proximal femur, and proximal fibula[6-8]. Clinical manifestations include pain, local swelling, effusion, and limited motion of the affected joint. The GCT of the distal fibula is extremely rare, with an incidence of less than 1%[9]. When GCTB is close to the joint, it poses challenges in the surgical management. Lesion resection, prosthesis replacement, or bone graft reconstruction are often used for salvage treatment, but the joint function can still decrease[1,10,11].

CASE PRESENTATION

Chief complaints

A 61-year-old man presented with progressive swelling of the left lateral malleolus accompanied by pain for half a year and aggravation for 2 wk.

History of present illness

Preoperative examination revealed that he had dilated cardiomyopathy with class 3 cardiac function.

History of past illness

The patient's past medical history was unremarkable.

Personal and family history

The patient denied any family history.

Physical examination

There was a long oval mass around the left lateral malleolus, about 10 cm × 6 cm in size. It had normal skin color, soft texture, deep tenderness, and a clear boundary. It had no mobility, and the pronation and rotation functions were limited.

Laboratory examinations

The results such as routine hematological testing, blood sedimentation rate, and tumor-associated markers were normal.

Imaging examinations

Plain radiographs revealed an expansile lytic lesion in the distal fibula (Figure 1). The ankle computed tomography also showed an expansile lytic lesion with the distal lateral cortex of the fibula invaded (Figure 2). A magnetic resonance imaging scan of his left ankle revealed not only a lytic lesion in the distal fibula but invasion of the soft tissue around the lateral malleolus as well (Figure 3).

FINAL DIAGNOSIS

Based on the clinical, radiological, and pathological findings (Figure 4), we confirmed the diagnosis of GCT of the distal fibula (Campanacci Grade III).

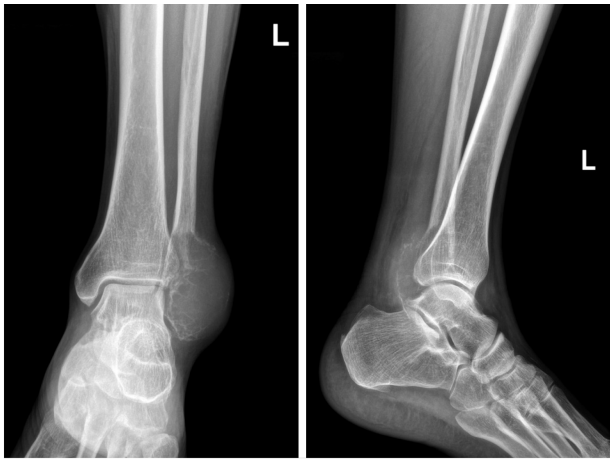

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Figure 1 Radiographs showed expansile lesion with soap bubble appearance.

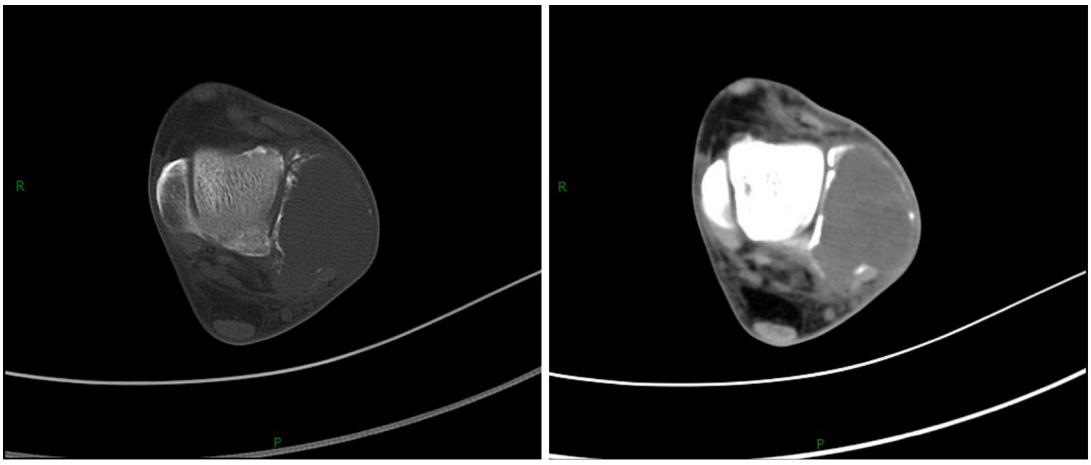

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Figure 2 Computed tomography showed the distal lateral cortex of the fibula was invaded.

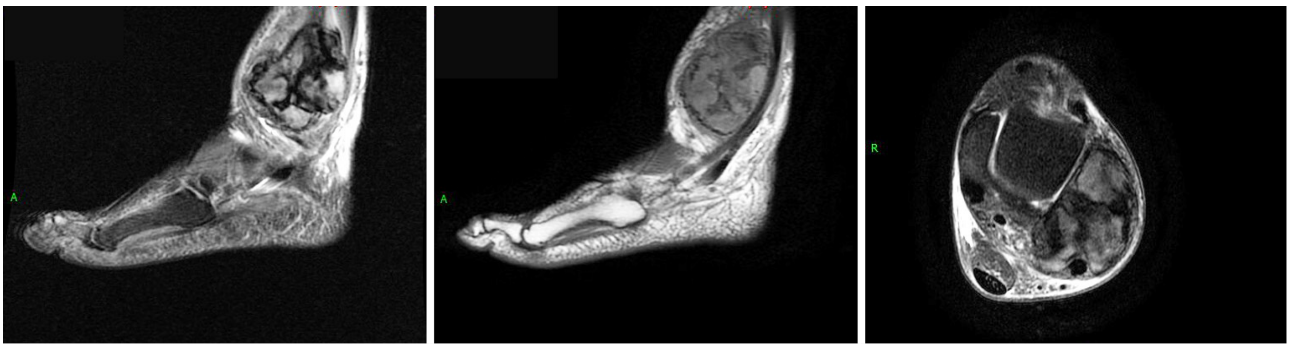

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Figure 3 Magnetic resonance imaging scan showed soft tissue around the lateral malleolus was also invaded.

TREATMENT

The individual therapeutic regimens were discussed and confirmed in a multidisciplinary clinic meeting. We offered three treatment options to the patient, including lesion resection combined with fibula head transplant to stabilize the lateral malleolus, 3D-printed prosthesis to reconstruction, or lesion resection and tibiotalus fusion. The options were discussed with the patient. Although the patient's heart function was poor, the anesthesiologists and cardiologists concluded that the patient

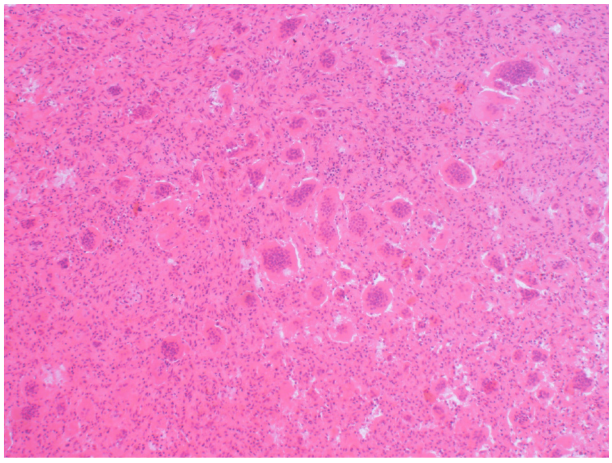

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Figure 4 Pathologically, the tumor comprised mononuclear stromal cells and multinuclear giant cells. Original magnification: × 100.

could tolerate the operation, but they recommended to minimize the operation time and the surgical trauma. Because the patient had low requirements for ankle joint function he opted for arthrodesis.

The incision was made along the lateral side of the left lateral malleolus, about 12 cm long. The biopsy incision was fusiform, and subcutaneous separation was performed. It was found that the tumor at the distal peroneal bone had a complete capsule with soft texture and poor mobility. The ligaments at the distal peroneal bone were all invaded and part of the brevis muscle was involved. However, the peroneal longus muscle was not involved. The mass was completely exposed 3 cm above the proximal end of the broken fibula, and the mass, distal ligaments, and soft tissues were completely removed along the fascia space of normal tissue (Figure 5). The joint surface of the medial malleolus was intact, and the tibia and talus were not invaded. The local soft tissue was soaked in distilled water for 10 min. The articular surfaces of the distal tibia and the talus were exposed and removed. After the subchondral bone was combined and flattened, 3 headless compression screws were pressed with compression forceps for fixation. The tibiotalar joint was fixed firmly without micromotion (Figure 6). Next, we sutured the remaining peroneus brevis to the peroneus longus muscle and attached it to the lateral fascia to stabilize the lateral ankle joint. The skin was trimmed, and the incision was sutured. Pressure dressing and plaster cast were used for 6 wk. After 6 wk the plaster was removed, and patient was permitted to partially bear weight. Three months later the patient progressed to full weight bearing.

OUTCOME AND FOLLOW-UP

The patient recovered smoothly after surgery, and the postoperative condition was stable. Three months later he began to walk normally. The patient was asymptomatic during the 2 years of follow-up after the operation. There was no recurrence, and he has had a satisfactory recovery (Figure 7). The patient was advised to continue to follow-up every 3-6 mo.

DISCUSSION

The lateral malleolus is an important part of the ankle joint, and its distal ligaments are very important for the stability and function of the ankle joint[12-14]. Once the lateral malleolus is invaded by a tumor, it will cause ankle joint dysfunction. GCTs on the bone of the distal fibula are extremely rare[9,15]. It usually occurs in people aged 20-40 years, and the most common sites are in the distal femur, proximal tibia, distal radius, and proximal humerus.

Standard GCT treatment is surgical removal, either by curettage or resection, combined with intraoperative adjuvant therapy[16]; however, some sites may not be amenable to resection, especially near the joint, such as the GCTs of the distal fibula[13,14,17]. Once the articular surface is invaded by a tumor, complete resection is necessary. Due to the importance of its anatomical structure, they are extremely difficult to treat once they occur, and currently there are no guidelines to adopt. Reconstruction treatment such as proximal fibula inversion, allograft, prosthetic replacement, *etc.* can restore the ankle function to the greatest extent, but external ankle ligament reconstruction has its corresponding difficulties, including soft tissue reconstruction and even rebuilding, and the ligament or tendon-bone healing is still difficult[18-20]. Furthermore, it can lead to long-term complications such as ankle arthritis, joint instability, and pain.

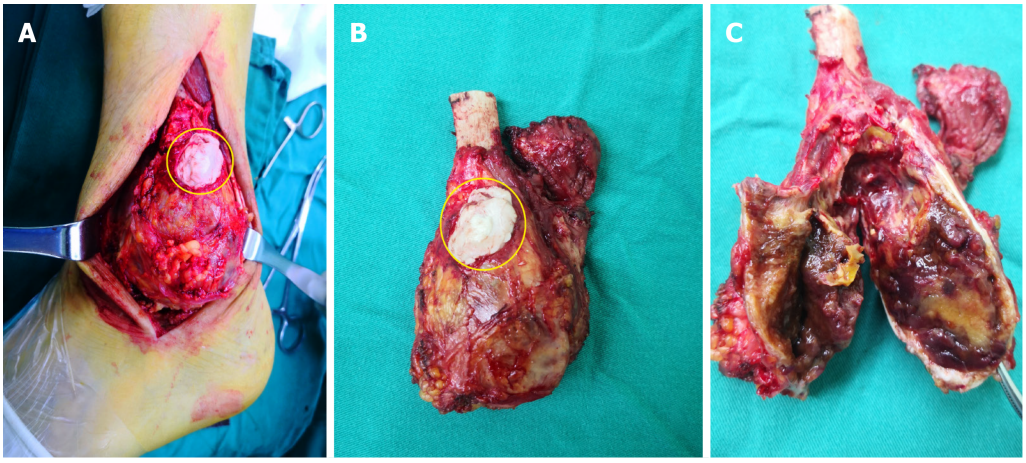

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Figure 5 The macroscopic piece for the tumor: fragile, yellowish-brown tumor tissue. A: Tumor *in vivo*; B: Tumor *in vitro*; C: Macroscopic bisection of tumor (yellow circles indicates the bone cement).

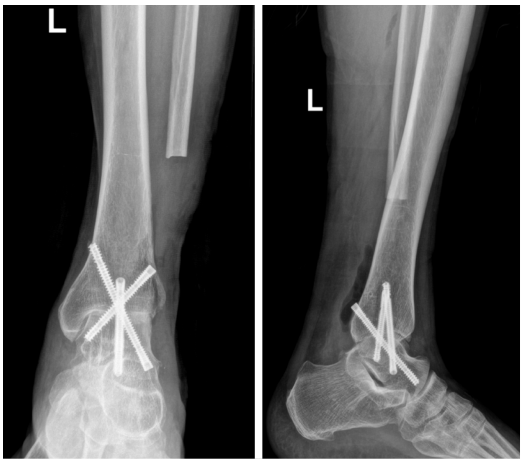

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Figure 6 Postoperative X ray showed the tibial talar joint was secured with three screws.

Although reconstructive surgery may improve ankle function, it is time consuming, requires a high cost for reconstruction surgery, and can induce traumatic arthritis, leading to dissatisfaction with the ankle function restoration. Arthrodesis reduces joint function; however the patient can walk without pain and the cost is lower. Therefore, there is no consensus on the best treatment modality. In this case, we first performed pathological biopsy on the patient. In order to avoid tumor spread, we used bone cement to seal the wound cavity. In the fusion procedure, we completely excised the mass and the soft tissue invaded by the tumor, sutured the normal peroneus brevis muscle to the peroneus longus muscle, and then sutured it to the deep fascia surrounding the lateral malleolus to enhance ankle stability. In our experience, arthrodesis is a good option[20].

Tibiotalar fusion and tibiotalocalcaneal fusion are two types of arthrodesis. Tibiotalar fusion is often used in young patients and in patients with good subtalar joints to preserve the range of motion of the subtalar joints[21,22]. Tibiotalar fusion is often used to reconstruct lateral stability, and in this case, the tibiotalar joint was fixed with three screws. The technique has the advantages of requiring less operation time, having a simple operation, and being reliable with effective fixation and good stability of the ankle joint. In addition, it is less invasive and less expensive than prosthetic replacement or reconstruction. After a 2-year follow-up, we concluded that tibiotalar joint fusion by screws was a good option for extensive resection of distal fibula tumors without anatomic reconstruction.

CONCLUSION

Although the lateral malleolus structure is important, limited excision will only increase the risk of

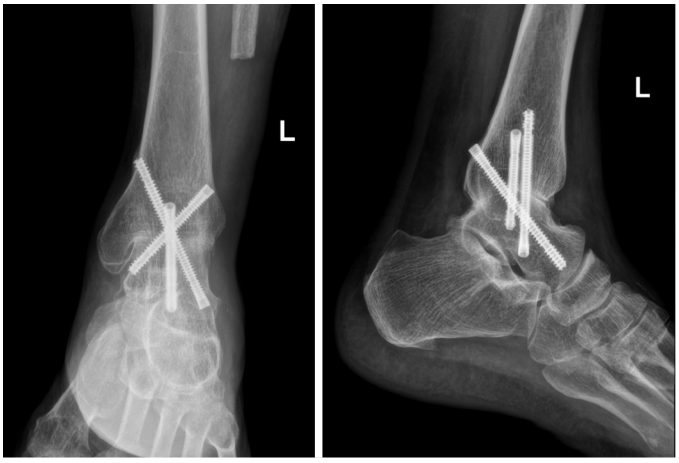

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Figure 7 X-ray 2 years after the operation showed osseous fusion of the tibial talus joint.

recurrence and pathologic fracture if the distal cortical and ligament structures are damaged by GCTB. Reconstruction can preserve ankle function as much as possible, but there are many complications. Although tibiotalar joint fusion loses the flexion and extension function of the ankle joint, it retains the ankle joint weight-bearing function and can ensure that patients bear weight without pain during walking. Therefore, it can be used as a surgical option for the treatment of distal fibular tumors.

FOOTNOTES

Author contributions: Fan QH and Long S wrote the manuscript and prepared the figures; Wu XK and Fang Q contributed to conceiving and designing the study and critically revised the manuscript; All authors read and approved the final manuscript.

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CASE REPORT

Repair of a giant inguinoscrotal hernia with herniation of the ileum and sigmoid colon: A case report

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Abstract

BACKGROUND

Giant inguinoscrotal hernias are huge inguinal hernias that extend below the midpoint of the inner thigh in the standing posture. Giant inguinoscrotal hernias are rare in developed countries because of their better medical resources and early treatment. However, they can develop in patients who refuse surgery or ignore their condition. Intervention is inevitable because strangulation and organ perforation can occur, leading to peritonitis and sepsis. Common surgical approaches include open abdominal and inguinal approaches or a combination of both.

CASE SUMMARY

We present the case of a 73-year-old man who visited our emergency department with a huge mass in his left scrotum and septic complications. Abdominal computed tomography revealed a large left inguinoscrotal hernia that contained small bowel loops and the colon. Emergency surgical intervention was performed immediately because intestinal strangulation was highly suspected. The operative repair was performed using a combination of mini-exploratory laparotomy and the inguinal approach. The incarcerated organs, which included the ileum and sigmoid colon, had relatively good intestinal perfusion without perforation or

ischemic changes. They were successfully reduced into the abdomen, and bowel resection was not necessary. A tension-free prosthetic mesh was used for the hernia repair. Two weeks after the initial surgery, and with adequate antimicrobial therapy, the patient recovered and was discharged from our hospital. No evidence of hernia relapse was noted during the outpatient follow-up examination 3 mo after surgery.

CONCLUSION
Emergency surgery involving combined mini-exploratory laparotomy and the inguinal approach should be performed for serious incarcerated giant inguinoscrotal hernias.

Key Words: Inguinal hernia; Ileum; Sigmoid colon; Sepsis; Hernia repair; Case report

Core Tip: Giant inguinoscrotal hernias are defined as hernias extending below the midpoint of the inner thigh of the patient in the standing position. Symptoms may vary, and serious complications, including intestinal obstruction and strangulation, may cause peritonitis and sepsis. Emergency surgery should be performed because of the risks of strangulation, perforation, and progressive necrosis. In this case, it was surprising to find the simultaneous existence of the ileum and sigmoid colon in the large inguinal hernia sac. The use of the inguinal approach combined with mini-exploratory laparotomy for giant hernial repair is beneficial and should be considered.

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INTRODUCTION

Giant inguinoscrotal hernias are defined as huge inguinal hernias that extend below the midpoint of the inner thigh in the standing posture[1]. Although rare, giant inguinoscrotal hernias still exist in developed countries. The main problem with inguinal hernias is their increasing size, which necessitates early surgical intervention. Giant inguinoscrotal hernias may develop in patients who refuse surgery or ignore their disease for a long time. Treatment of inguinoscrotal hernias is inevitable because strangulation and organ perforation can occur, resulting in further peritonitis and sepsis[2]. The World Society of Emergency Surgery (WSES) guidelines for emergency repair of complicated abdominal wall hernias suggest that patients should undergo emergency hernial repair immediately if intestinal strangulation is suspected[3]. Additionally, it has been proven that emergency surgical interventions are associated with higher rates of postoperative complications and adverse outcomes compared to early elective procedures[3,4]. We report the case of a patient with a giant inguinoscrotal hernia and herniation of the ileum and sigmoid colon without early surgical intervention who presented with sepsis and suspected bowel strangulation. The emergency repair was performed using a combination of mini-exploratory laparotomy and the inguinal approach.

CASE PRESENTATION

Chief complaints

A 73-year-old man visited the emergency department of our hospital because of a huge mass in his left scrotum and intolerable lower abdominal and groin pain for a duration of approximately 2 wk.

History of present illness

Approximately 20 mo prior, the patient was diagnosed with a huge left inguinoscrotal hernia at our outpatient department; however, he refused early surgical intervention. Several days before the patient presented to the emergency department, he also experienced general weakness and decreased urine output.

History of past illness

Other than the previous diagnosis of left inguinal hernia, the patient had no history of chronic diseases or surgeries.

Personal and family history

The patient had been working as a security guard at an apartment for more than 10 years. Part of his job involved lifting and carrying packages received by the residents. No relevant family history was noted.

Physical examination

His vital signs were as follows: Body temperature, 36°C; blood pressure, 106/73 mmHg; heart rate, 95 beats/min, and respiratory rate, 22 breaths/min. The results of the physical examination revealed pitting edema of the bilateral lower limbs, tenderness in the left lower abdomen and inguinal region, a large irreducible inguinoscrotal hernia on the left side that measured approximately 14 cm x 16 cm in the supine position, and bilateral inguinal ecchymosis (Figure 1).

Laboratory examinations

Laboratory serum examinations revealed a white blood cell count of 21.57 × 10^3/μL, 92.3% neutrophils, and thrombocytopenia with a platelet count of 90 × 10^3/μL. C-reactive protein and procalcitonin levels were 35.32 mg/dL and 24.96 ng/mL, respectively. The serum creatinine level was 2.3 mg/dL.

Imaging examinations

Abdominal computed tomography (CT) scanning was performed without contrast because of decreased renal function, suggesting a huge left inguinal hernia with herniation of the small intestine and colon as well as a small number of ascites (Figure 2).

FINAL DIAGNOSIS

Physical and laboratory serum test results and radiographic findings indicated the presence of a large incarcerated inguinal hernia with sepsis.

TREATMENT

After diagnosing, we intravenously administered antibiotics comprising Flomoxef 1g every 12 h. Flomoxef was chosen because of its efficacy for intra-abdominal infections. The dosage was adjusted according to the patient's creatinine clearance rate. Because of the risks of strangulation, perforation, and further profound septic shock, emergency surgery was performed.

The patient was placed in the supine position under general anesthesia. An inguinal incision on the left side revealed that the hernial sac was filled with ileum and sigmoid colon. Because of the failure to reduce the contents into the abdominal cavity, even with enlargement of the internal ring, a mini-midline incision was made. The incarcerated organs were carefully pulled out, and the adhesion between the hernial contents was separated. The hernial contents were grossly inflamed, with mild swelling and an erythematous appearance (Figure 3A). The incarcerated organs, with relatively good intestinal perfusion and no perforation or ischemic changes following a thorough examination, were successfully reduced into the abdomen (Figure 3B). The hernial repair was performed using tension-free techniques with unabsorbable polypropylene mesh sutured on the posterior wall of the inguinal canal. Finally, a Jackson-Pratt drain was placed in the left inguinal canal. The patient was transferred to the intensive care unit after surgery to closely monitor the end-organ function.

OUTCOME AND FOLLOW-UP

The patient experienced no complications during the early postoperative period. Two weeks after the initial surgery, with adequate infection control, the patient recovered and was discharged. The patient was able to remain in the standing position without evidence of relapse of the hernia at the time of the outpatient follow-up examination 3 mo after surgery.

DISCUSSION

Giant inguinoscrotal hernias are rare in developed countries. However, they can occur as a complication

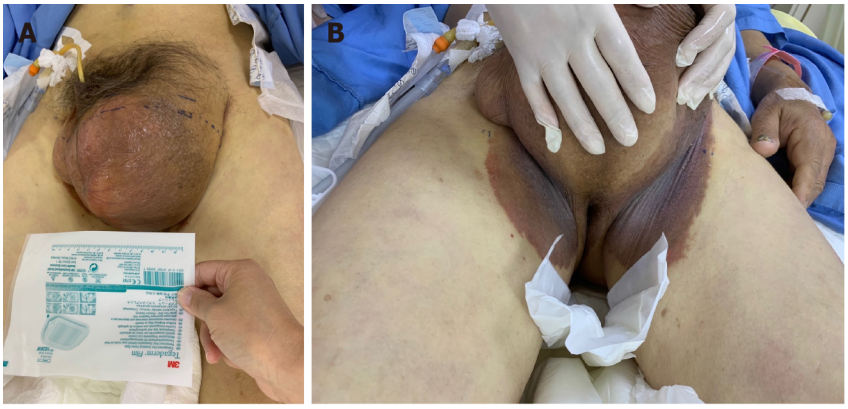

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Figure 1 Left-side giant inguinoscrotal hernia. A: Huge irreducible inguinoscrotal hernia with the penis buried within the enlarged scrotum; B: Ecchymosis formation in the bilateral inguinal region.

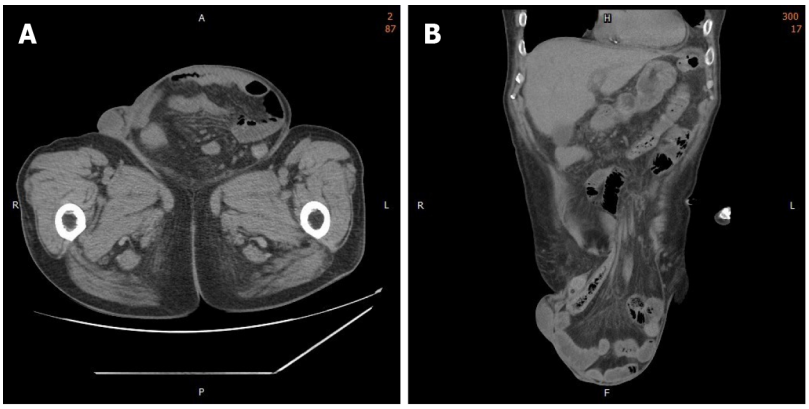

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Figure 2 Abdominal computed tomography scan. A: Computed tomography (CT) of the abdomen (axial section); B: CT scan of the abdomen (coronal section) revealing a large left-side inguinal hernia containing small bowel loops as well as the colon.

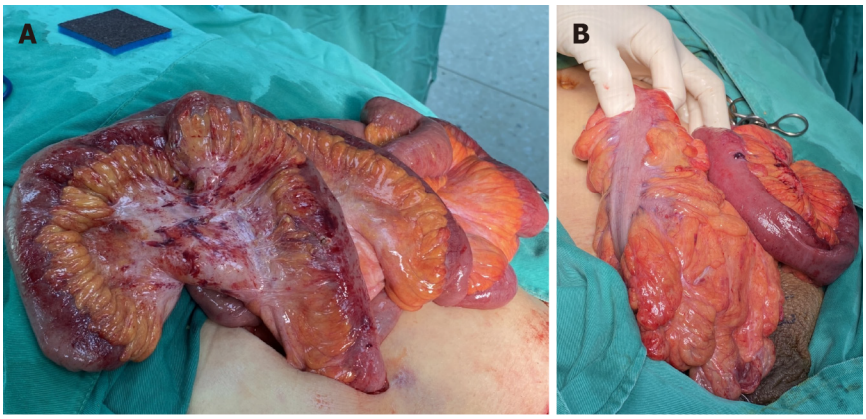

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Figure 3 Intraoperative findings. A: Hernial contents are grossly inflamed, with mild swelling and an erythematous appearance; B: The ileum and sigmoid colon from the hernial sac with relatively good perfusion.

of an inguinal hernia. Other complications of an inguinal hernia include hernial enlargement, increasing pain, and incarceration or strangulation. They often result from patient neglect and the rejection of the suggested surgery for a hernia. For our patient, the risk factors for inguinal hernia were identified as his age, sex, and occupation[5]. Giant inguinoscrotal hernias are more common in less developed countries that lack medical resources. The size of the hernia often negatively affects daily activities. The penis buried in the enlarged scrotum can result in urine dribbling over the scrotal skin, potentially leading to

skin damage, ulceration, and further infections[6]. Giant inguinoscrotal hernias accompanied by acute kidney injury resulting from urinary tract obstruction have been reported[7,8]. In the present case, the CT scan did not reveal obstructive uropathy such as hydronephrosis. Hence, we suspected that renal impairment with the clinical presentation of decreased urine output in our case occurred as a result of sepsis. Hernial contents that cannot be reduced into the abdominal cavity are referred to as incarcerated hernias. Bowel obstruction and strangulation of the bowel contents with a compromised blood supply are serious results of incarceration. The common contents of the hernial sac are the small intestine and omentum. In some cases, the stomach, appendix, cecum, kidney, urinary bladder, ovaries, and sigmoid colon have been found in the hernial sac[9,10]. In the present case, the simultaneous existence of the ileum and sigmoid colon in a large inguinal hernia sac was observed.

In our patient with a giant inguinoscrotal hernia, sepsis occurred with impaired renal function and coagulation according to the Sequential Organ Failure Assessment score[11]. We performed surgery immediately because of the risk of strangulation and progressive necrosis, which could be fatal according to the WSES guidelines for emergency repair of complicated abdominal wall hernias[3].

A sudden increase in intra-abdominal pressure may occur after the majority of the hernial organs have been reduced into the abdominal cavity[12]. Abdominal compartment syndrome can develop, leading to respiratory compromise attributable to an increase in intrathoracic pressure[13]. To avoid compromising respiratory and cardiac functions and enable successful recovery, a complete preoperative evaluation and careful postoperative monitoring are important.

Several surgical interventions have been developed for this purpose, and they all share the common strategy of relocating the hernial organs into the abdominal cavity, adapting to a relative emptiness. Two approaches can be employed. First, the abdominal cavity can be increased by artificially inducing progressive pneumoperitoneum[14,15]or creating an anterior abdominal wall defect and performing mesh repair and flap techniques[16,17]. Second, reduction of abdominal or hernial contents can be performed to relocate the reduced abdominal organs[18].

In the present case, bowel resection was not necessary because the patient maintained an acceptable abdominal space without excessive tension and airway pressure perioperatively. Furthermore, his vital signs and urine output were closely monitored postoperatively because of the high risk of increased intra-abdominal pressure. Although measuring the intravesical pressure is a common method used to identify intra-abdominal pressure, we did not use this for our patient because of its relatively invasive nature despite the minimally invasive implementation requirements. Orchiectomy was not performed because dissection of the spermatic cord was not problematic. The scrotal skin was not resected because it was not infected. We successfully predicted that the skin would be able to recover after the removal of additional tension caused by the giant inguinoscrotal hernia.

We used an inguinal approach combined with a mini-midline incision. This method of management has several advantages. First, it results in an easier reduction of the ileum and sigmoid colon into the abdominal cavity through the defect. Second, it allowed us to carefully examine the bowel condition to determine the presence of perforation or ischemic changes. Finally, a Jackson-Pratt drain could be placed to ensure adequate drainage. Because hernial defects are large, the risk of recurrence of giant inguinoscrotal hernias is much higher than that of other inguinoscrotal hernias. The use of tension-free techniques whenever possible is recommended for hernial repairs[19]. Most importantly, in addition to the initial surgical intervention, appropriate antimicrobial therapy was fundamental for our patient with sepsis.

CONCLUSION

In modern surgical practice, giant inguinoscrotal hernias are uncommon. When they do occur, they present challenges for the attending surgeon because they can cause fatal complications. For patients presenting with sepsis, emergency surgery should be performed if there is significant incarceration or strangulation. Adequate preoperative planning as well as intraoperative and postoperative monitoring are essential for these patients. The use of a combination of mini-exploratory laparotomy and the inguinal approach is worthy of further investigation. Enlargement of the abdominal cavity or debulking of the abdominal organs should be avoided if the abdominal cavity is sufficient. Relocation of the incarcerated organs using proper and early antimicrobial therapy was the cornerstone of successful treatment for this case.

FOOTNOTES

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CASE REPORT

Anti-leucine-rich glioma inactivated protein 1 encephalitis with sleep disturbance as the first symptom: A case report and review of literature

De-Lian Kong

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Abstract

BACKGROUND

Anti-leucine-rich glioma inactivated protein 1 (anti-LGI1) encephalitis is an infrequent type of autoimmune encephalitis (AE) characterized by acute or subacute cognitive and psychiatric disturbance, facio-brachial dystonic seizures (FBDSs), and hyponatremia. Anti-LGI1 AE has increasingly been considered a primary form of AE. Early identification and treatment of this disease are clearly very important.

CASE SUMMARY

Here, we report that a male patient developed severe anti-LGI1 encephalitis, which was initially misdiagnosed as a sleep disturbance. He was hospitalized for epileptic seizures and typical FBDSs half a month after he developed sleep disturbances. LGI1 antibodies were detected in his cerebrospinal fluid and serum (1:100 and 1:3.2, respectively), which led to the diagnosis of classic anti-LGI1 AE. No obvious abnormality was observed on brain computed tomography images. T2-weighted fluid-attenuated inversion recovery and T2-weighted scans of brain magnetic resonance imaging (MRI) showed slightly elevated signals within the left basal ganglia area. No tumor was detected within the brain of this patient using MRI. After hormone and antiepileptic drug treatment, the patient's symptoms improved significantly.

CONCLUSION

Anti-LGI1 antibody-associated encephalitis has characteristic clinical manifestations, such as cognitive impairment, psychiatric symptoms, seizures, sleep disorders, hyponatremia, and FBDSs. LGI1 antibodies are present in the serum and/or cerebrospinal fluid, but their production is sensitive to immunosuppressants, and this disease has a relatively good prognosis. In particular, we should be aware of the possibility of anti-LGI1 antibody-associated encephalitis in

adolescents with sleep disorders to avoid missed diagnoses and misdiagnoses.

Key Words: Leucine-rich glioma inactivated 1 antibody; Autoimmune encephalitis; Sleep disturbance; Seizures; Facio-brachial dystonic seizures; Case report

Core Tip: Anti-leucine-rich glioma inactivated protein 1 (anti-LGI1) encephalitis is a rare autoimmune encephalitis (AE) characterized by acute or subacute cognitive impairment, facio-brachial dystonic seizures, psychiatric disturbances and hyponatremia. Herein, we report that a male patient developed severe anti-LGI1 encephalitis, which was initially misdiagnosed as sleep disturbance. He had antibodies targeting LGI1 both in his cerebrospinal fluid and serum, which led to the diagnosis of typical anti-LGI1 AE. The case indicated that we should be aware of the possibility of LGI1 antibody-associated encephalitis to avoid missed diagnoses and misdiagnoses especially in adolescents with sleep disorders.

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INTRODUCTION

In general, the phrase autoimmune encephalitis (AE) is defined as diseases caused by antigen-antibody reactions of the immune system to the central nervous system[1]. The main clinical manifestations of AE are acute or subacute epileptic seizures, facio-brachial dystonic seizures (FBDSs), cognitive disturbances, and mental disorders.

Sleep dysfunction in patients with AE has received little attention and is most likely neglected because clinicians pay more attention to neurological and psychiatric symptoms. Nevertheless, sleep disorders are very common in AE patients and often persist beyond the acute stage, which seriously affects patients' quality of life. All patterns of somnipathy can arise in AE patients due to the influence of the disease on an extensive number of brain networks participating in sleep initiation and regulation. Anti-IgLON5 and anti-N-methyl-d-aspartate (NMDA) receptor encephalitis are two representative diseases in which sleep disturbances are common and serious. Somnipathy varies according to the disease stage in anti-NMDA receptor encephalitis, and the core symptom in anti-IgLON5 disease is sleep disorders[2].

However, few reports described sleep disorders associated with anti-leucine-rich glioma inactivated protein 1 (anti-LGI1) antibody encephalitis. Anti-LGI1 antibody-associated encephalitis is a type of AE that is characterized by epilepsy, a recent memory decline, and mental and behavioral abnormalities as its main clinical manifestations. Since anti-LGI1 encephalitis is a recently identified disease, limited data are available on its clinical manifestation, especially in patients presenting with sleep disturbances as the initial symptom. Here, we report a patient who developed severe anti-LGI1 encephalitis, which was initially misdiagnosed as a sleep disorder. The patient was hospitalized for epileptic seizures and typical FBDSs half a month after he developed the sleep disturbance.

CASE PRESENTATION

Chief complaints

Sleep disorders, sudden limb convulsions with unconsciousness.

History of present illness

This patient initially visited the doctor because he suffered from suddenly persistent insomnia (with difficulties initiating and especially maintaining sleep). Dream enactment and somniloquy occurred during his sleep, and he felt fatigue and weakness after waking in the morning. The doctor prescribed some sleeping pills. No significant improvement was observed after taking the medicine for several days. Half a month later, his right hand twitched involuntarily in the evening before admission when he had his hair cut; this symptom lasted for approximately 3 s and was not given much attention. After waking the next morning, he had two other attacks with intervals of approximately half an hour, lasting approximately 3–5 s each. Then, secondary limb convulsions appeared as follows: Flexion of both upper

limbs, ankylosis of both lower limbs, unconsciousness, eyes turning up, crown closure, and mouth foaming, which lasted for approximately five minutes. Immediately, the patient's consciousness became lucid, and after waking, he could not recall the course of the disease and experienced slight dizziness and headache

Then, he went to the emergency department of our hospital. He was administered an intravenous injection of "mannitol, acetylglutamine and sodium acetate ringer" after brain computed tomography (CT) scan, which showed no obvious abnormality. Then, intermittent involuntary twitching of the right hand was still present, which occurred once in approximately 1-2 h and lasted 3-5 seconds each time. The patient was admitted to our hospital for further diagnosis and treatment.

History of past illness

He had previously been healthy.

Personal and family history

There is no history of familial genetic diseases.

Physical examination

The neurological examination showed no obvious abnormality.

Laboratory examinations

The white blood cell count (11.23 × 10^9 cells/L) and neutrophil percentage (89%) increased significantly in the full blood count. All biochemical indexes and thyroid function were normal or negative.

Cerebrospinal fluid (CSF): A routine CSF examination displayed acellular fluid. No bacterial growth or abnormal biochemistry was observed in the CSF. The opening pressure was not abnormal. CSF cytology showed that the percentage of leukocytes in multiple nuclei increased by 50% (reference value 0%–6%), and the other indexes were normal.

Detection of autoimmune antibodies: LGI1 antibodies were examined and were positive in both the serum and cerebrospinal fluid (1:100 and 1:3.2, respectively), and other antibodies (contactin-associated protein 2 (CASPR2), N-methyl-D-aspartate receptor (NMDAR), glutamic acid decarboxylase (GAD65), GABA, and AMPA1) were negative (Figures 1 and 2), which confirmed the diagnosis.

No abnormalities in hepatitis B surface antibody test results. Human immunodeficiency virus antibodies and *Treponema pallidum*-specific antibodies were normal or negative.

Imaging examinations

A computed tomography (CT) scan of the thorax showed inflammation of the right lower lobe of the lung. No abnormality was detected on the brain CT scan.

Brain magnetic resonance imaging (MRI) (Figure 3) results: An abnormal shadow signal was observed in the left basal ganglia area, which displayed a high signal in T2-weighted fluid-attenuated inversion recovery (FLAIR) MRI and T2-weighted MRI.

Video electroencephalogram (EEG) (Figure 4): The patient's EEG was mildly abnormal. Multiple slow wave bursts were observed during wakefulness. Interference artifacts may have been present.

FINAL DIAGNOSIS

Clinicians must determine the correct diagnosis as early as possible, and excluding the presence of an underlying malignancy is certainly worthwhile because it may be associated with this pathology[3]. In this case, no signs suggested the presence of neoplasia.

In this case, a series of clinical manifestations, such as sleep disorders, seizures, and typical FBDCs, combined with abnormal signals of brain MRI and positive LGI1 antibodies in blood and cerebrospinal fluid prove that this case conforms to the diagnosis of anti-LGI1 autoimmune encephalitis.

TREATMENT

Immunotherapy was initiated with dexamethasone, and a continuous intravenous infusion of sodium valproate was administered to control the seizures.

OUTCOME AND FOLLOW-UP

No major seizures occurred during hospitalization, but intermittent FBDSs persisted during the first several days after hospitalization. One week later, FBDSs did not appear. Two weeks later, the patient's

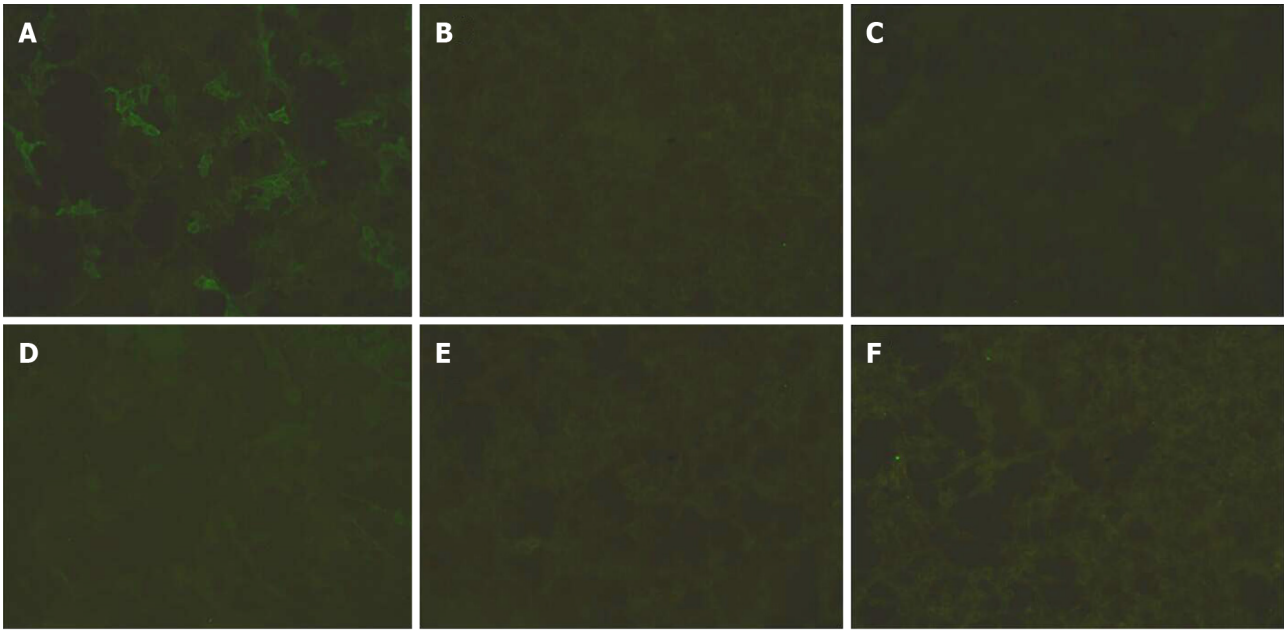

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Figure 1 LGI-1(A), CASPR2(B), NMDAR(C), GAD65(D), GABA(E), AMPA1(F) antibodies in CSF validated by cell-assay of transfected cells. LGI1-IgG in CSF (1:3.2) were positive but others (CASPR2, NMDAR, GAD65, GABA, AMPA1) were negative.

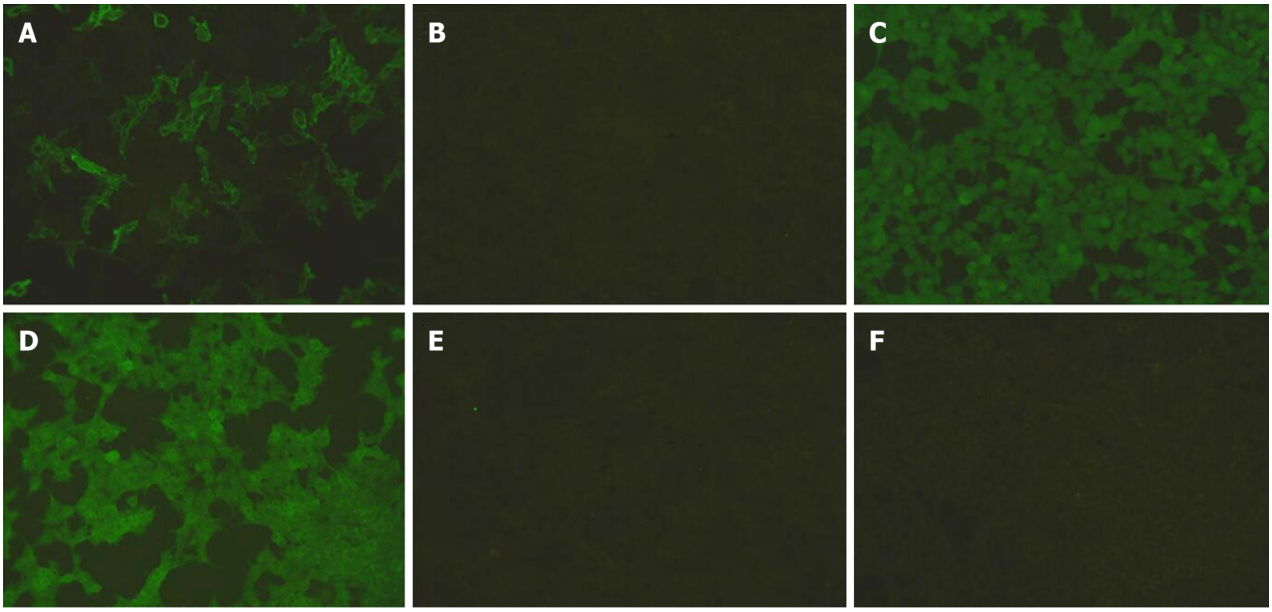

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Figure 2 LGI-1(A), CASPR2(B), NMDAR(C), GAD65(D), GABA(E), AMPA1(F) antibodies in serum validated by cell-assay of transfected cells. LGI1-IgG in serum (1:100) were positive but others (CASPR2, NMDAR, GAD65, GABA, AMPA1) were negative.

symptoms improved significantly, and thus he was discharged and was told to gradually reduce the dose of prednisone after discharge. During hospitalization, the patient's sleep disturbances gradually decreased, and the patient's sleep completely returned to normal at discharge. The patent was discharged with antiepileptic therapy and corticosteroid. He is followed up every three months and symptoms have not recurred.

DISCUSSION

The incidence and mortality rates of encephalitis are 8%-18.45%[4-7]. The disease has been recognized

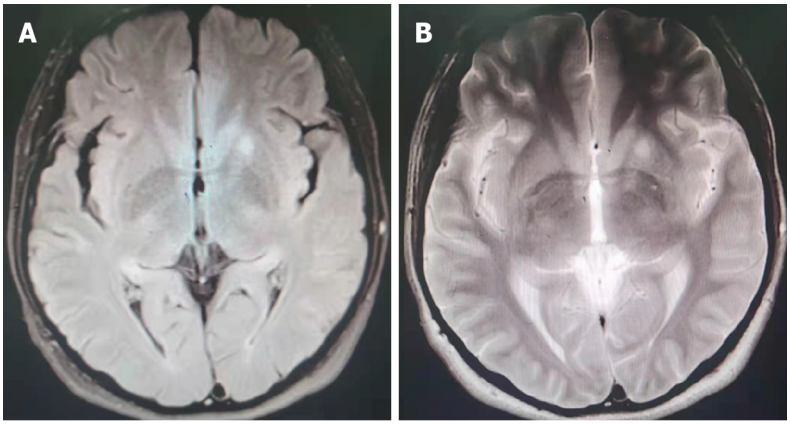

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Figure 3 Brain magnetic resonance images of this patient. A: T2-weighted fluid-attenuated inversion recovery showed slightly elevated signals within the left basal ganglia area; B: T2-Weighted scans showed slightly elevated signals within the left basal ganglia area.

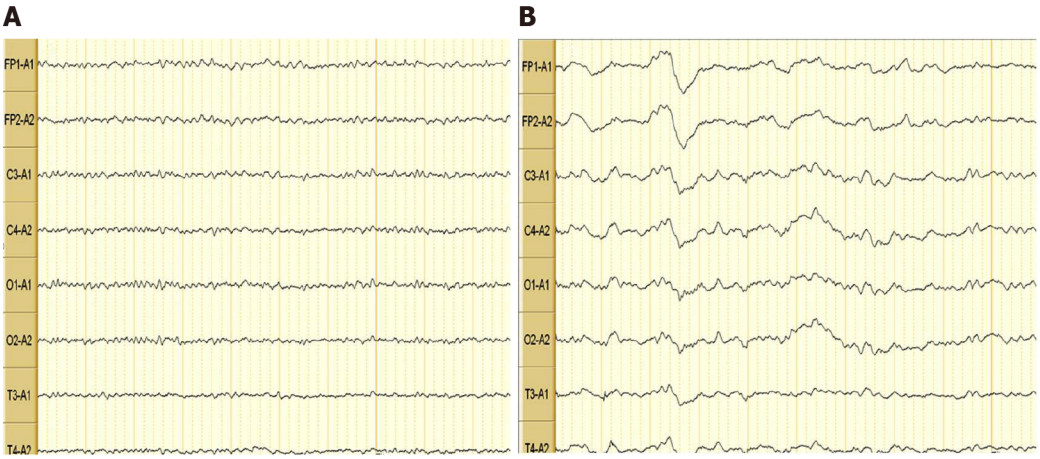

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Figure 4 Video electroencephalography of this patient. A: Wakefulness and eyes closed; B: Sleep state: Mildly abnormal electroencephalography. Multiple slow wave bursts during wakefulness. There may have been interference artifacts.

by an increasing number of clinicians since the first case of teratoma-related anti-NMDA receptor encephalitis was reported in 2007[8].

Dalmau *et al*[9] were the first to report that anti-NMDAR encephalitis has a close relationship with teratoma in 2007. Lai *et al*[10] first discovered anti-AMPA receptor encephalitis in 2009, and Lancaster *et al*[11] identified anti-GABABR encephalitis in 2010. Anti-LGI1 antibody encephalitis and anti-CASPR2 antibody encephalitis were first discovered by Lai *et al*[12] in 2010. Anti-LGI1 encephalitis is infrequently associated with tumors, and most patients recovered after treatment with steroids or other immunotherapies[13].

A survey discovered that AE substantially affected the patients' quality of life[14]. The diagnosis of AE is very difficult due to its sophisticated clinical symptoms[15]. The key to the diagnosis of AE is a neuronal autoimmune antibody, and a close relationship has been observed between the difference in the antibody titer and its clinical course[16].

The main manifestations of anti-LGI1 encephalitis are epilepsy, cognitive and mental disorders, hyponatremia, and sleep disorders, and explanations are provided below.

Epilepsy

Among the patients positive for LGI antibodies, twenty percent-forty percent[17] have FBDSs, which are short, frequent, and unconscious seizures, together with dystonia, simple upper limb spasm and contraction, and ipsilateral face twitch (not long, 3 s, several times a day). Some scholars[18] postulate that FBDSs might be dystonic. However, Irani *et al*[19] and other scholars proposed that FBDSs were a type of epileptic seizure.

Previous studies have discovered that ninety percent of patients have seizures that primarily present in the following three types: FBDS, focal to bilateral tonic-clonic seizure and mesial temporal lobe

epilepsy -like seizure[20-26]. In a recent study, patients with anti-LGI1 AE were divided into the following three groups according to the epilepsy symptomatology: FBDS alone (FBDS-only), epileptic seizures without FBDS [non-FBDS], and coexistence of FBDS and other seizures (FBDS+)[27]. Researchers found that FBDSs were significantly decreased and even vanished after treatment with oral steroids[28]. Basal ganglia lesions are present in patients with FBDSs[1].

FBDSs are the particular seizure type experienced by anti-LGI1 AE patients, and probably half of the patients experience FBDSs[20,21,22,19,29]. FBDSs are easy to identify and diagnose; however, EEG shows abnormalities during onset in only a few patients[19,29]. The origin of FBDSs remains controversial. Cortical, subcortical, and cortical-subcortical origins have been shownby distinct studies[27,30,31]. A study on anti-LGI1 AE[18] concluded that anti-LGI1 antibodyassociated encephalitis commonly damaged the hippocampus and basal ganglia, which was slightly different from a previous study that discovered that the motor cortex and hippocampus may be two main targets in anti-LGI1 AE[24,20]. In addition, immunotherapy reduces epileptic seizures and prevents complications[32]. A study[33] reported high T2 and FLAIR signals in the bilateral temporal lobe and hippocampus on brain MRI[18]. This finding is consistent with the report that LGI1 is primarily expressed in the temporal cortex and hippocampus.

The seizure form experienced by this patient FBDS+, and the symptoms were obviously relieved after treatment with hormone and antiepileptic drugs, consistent with the characteristics of anti-LGI1 encephalitis.

Cognitive and mental impairment

Previous studies discovered that approximately ninety-five percent of patients suffered from cognitive dysfunctions. Majoie *et al*[34] discovered that eighty-nine percent of LE patients had dysmnesia. Malter *et al*[17] identified relationships between cognitive impairment and the disease course before immunotherapy.

The main manifestations of mental/behavioral disturbances are individual and behavioral abnormalities, such as prone to anger, anxiety, impulsive behavior, and hallucinations[18,35]. Serum anti-LGI1 antibodies may remain detectable after full clinical recovery[36]. A similar mechanism[35] can be hypothesized in anti-LGI1 encephalitis because the LGI1-ADAM22-AMPAR interaction is proposed to influence long-term depression (LTD)[37,38]. As LTD is also essential for spatial memory, disruption of this process might explain the spatial disorientation observed in patients with anti-LGI1 encephalitis.

Hyponatraemia: As reported, hyponatraemia occurs in sixty percent of patients with LGI1 AE[21,18]. The main reason was regarded as abnormal secretion of antidiuretic hormones, which will be correlated with simultaneous LGI1 expression in the hypothalamus and kidney.

Brain MRI: Most LE patients presented abnormal T2 and FLAIR signals in bilateral temporal lobe regions on brain MRI, and a small proportion of patients showed abnormal signals in one side of the hippocampus. Furthermore, the lesions often involve the temporal lobe and basal ganglia[39]. In some patients with FBDSs, high T1/T2 are detected signals on brain MRI[40] and high FDG-PET metabolism has been observed in the basal ganglia[19].

In our case, FLAIR and T2-weighted scans showed slightly elevated signals within the left basal ganglia area, consistent with the characteristics of anti-LGI1 encephalitis detected using MRI.

Sleep disturbances: Sleep disturbances are also common in patients with AE[41]. Sleep dysfunctions have also been described in association with various neuron-specific antibody biomarkers, including IgLON5, LGI1, CASPR2, NMDA receptor, and Ma2. There are four forms of sleep disorders: rapid eye movement sleep behavior disorder, hypersomnia, fragmented sleep, and sleep-disordered breathing. New sleep complaints (*e.g.*, gasping and snoring) were reported by seventy-three percent of AE patients in one study[42].

LGI1 is a glycoprotein located in the synapse and primarily expressed in the neocortex and hippocampus[43]. A recent study of PSG revealed that sleep efficiency, total sleep time, N3 sleep and REM sleep decreased significantly in anti-LGI1 encephalitis patients[44]. Another study[45] demonstrated that sleep efficiency and total sleep time were obviously reduced in anti-LGI1 AE patients. An imbalanced sleep structure was discovered, showing ascended N1, reduced N3, REM components and an abnormal N2 structure. These findings were not related to nocturnal episodic events or the presence of sleep hyperkinetic movements. Animal experiments have shown that LGI1 antibodies play a neurotoxic role, potentially mediated through the reduction in calcium currents and induction of apoptosis[46]. The LGI1 gene is widely expressed in the hypothalamus, including the ventromedial nucleus[47]. The ventromedial nucleus contains glycine/GABA neurons and receives direct synaptic input from glutamatergic neurons in the sublaterodorsal tegmental nucleus. Studies have shown that silencing this circuit may lead to REM sleep without atonia[48]. Antibodies binding to hypothalamic neurons may result in hypothalamic disturbances, likely leading to RBD and insomnia. Clinical and PSG outcomes improved after immunotherapy[49].

However, other authors[50,51] found that the chief immunological targets of anti-LGI1 encephalitis are the motor cortex, limbic system, brainstem and striatum thalamus, consistent with the findings that LGI1 is broadly expressed in neurons and some axonal terminals throughout the Central Nervous

System.

In this case, the manifestations of sleep disorders were persistent insomnia (with difficulties initiating and especially maintaining sleep), dream enactment and somniloquy, which lasted for half a month before the seizures began. Furthermore, sleep disorders responded poorly to general sleeping pills, and the symptoms were relieved rapidly after immunotherapy, consistent with the characteristics of sleep disorders in AE.

In conclusion, sleep disturbance, marked by symptoms including sleep fragmentation, dream enactment behaviors and ambiguous or total loss of physiological sleep rhythms, could be a visible and inherent characteristic of anti-LGI1 encephalitis.

Improving the detection of sleep disorders is conducive to the early detection of anti-LGI1 AE, especially in patients presenting with sleep disorders as the initial symptoms; this approach may prevent missed diagnoses and misdiagnoses. Additionally, this approach may allow patients to receive treatment as soon as possible and promote the early recovery of patients.

EEG: Usually, a specific change in EEG is not observed in patients with anti-LGI1 AE. The abnormal EEG for FBDSs is probably caused by a deeply located or highly localized epileptogenic zone[21,23].

CONCLUSION

The case report illustrates the importance of antibody testing and early recognition of sleep disturbances in identifying this condition, which is often undiagnosed. Early recognition and initiation of therapy are important in the management of patients with anti-LGI1 AE and their prognosis and may both prevent perpetual neurological impairment and improve long-term outcomes. Unfortunately, polysomnography and FDG-PET were not completed due to the limitations of our hospital's facilities. In a future study, we will try to collect these data.

FOOTNOTES

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CASE REPORT

Fat-poor renal angiomyolipoma with prominent cystic degeneration: A case report and review of the literature

Shi-Qi Lu, Wei Lv, You-Jun Liu, Huan Deng

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Abstract

BACKGROUND

Angiomyolipoma (AML), the most common benign tumor of the kidney, is usually composed of dysmorphic blood vessels, smooth muscle, and mature adipose tissue. To our knowledge, AML with cystic degeneration has rarely been documented. Cystic degeneration, hemorrhage, and a lack of fat bring great challenges to the diagnosis.

CASE SUMMARY

A 60-year-old man with hypertension presented with a 5-year history of cystic mass in his left kidney. He fell 2 mo ago. A preoperative computed tomography (CT) scan showed a mixed-density cystic lesion without macroscopic fat density, the size of which had increased compared with before, probably due to hemorrhage caused by a trauma. Radical nephrectomy was performed. Histopathological studies revealed that the lesion mainly consisted of tortuous, ectatic, and thick-walled blood vessels, mature adipose tissue, and smooth muscle-like spindle cells arranged around the abnormal blood vessels. The tumor cells exhibited positivity for human melanoma black-45, Melan-A, smooth muscle actin, calponin, S-100, and neuron-specific enolase, rather than estrogen receptor, progesterone receptor, CD68, and cytokeratin. The Ki-67 labeling index was less than 5%. The final diagnosis was a fat-poor renal AML (RAML) with prominent cystic degeneration.

CONCLUSION

When confronting a large renal cystic mass, RAML should be included in the differential diagnosis.

Key Words: Kidney; Angiomyolipoma; Cystic degeneration; Pathogenesis; Diagnosis; Case report

Core Tip: Angiomyolipoma (AML) is a clinically common benign kidney tumor. The majority of classic AMLs can be diagnosed preoperatively through radiological technology because of the appearance of an adipose component. We report a rare case of a fat-poor renal AML (RAML) with prominent cystic degeneration. The establishment of RAML diagnosis is challenging because of the lack of specificity of imaging features. Histopathological and immunohistochemical examinations show that the three classic components express AML markers, supporting the final diagnosis.

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INTRODUCTION

Angiomyolipoma (AML), also called hamartoma, is the most common benign kidney tumor. Fischer first described this tumor in 1911 with distinctive pathologic features, including dysmorphic blood vessels, smooth muscle, and mature adipose tissue[1]. The histogenesis of AML is still a matter of debate because hard evidence is lacking. Perivascular epithelioid cells (PECs) are traditionally considered as the principal cellular source of AML. Thus, it is also considered as a part of the PEComa family. AML can occur sporadically or in association with the tuberous sclerosis complex or, more rarely, sporadic lymphangioleiomyomatosis[2]. On the pathological basis of the elastin-poor, tortuousand ectatic vascular structures that readily tend to rupture, the most dangerous complication of renal AML (RAML) is hemorrhage (Wunderlich's syndrome[3]), occurring spontaneously or induced by trauma. The majority of classic AMLs can be diagnosed preoperatively by using radiological technology because of the appearance of an adipose component. However, when adipose tissue is absent or hemorrhage occurs, the diagnosis may become challenging. We present a case of RAML with prominent cystic degeneration and little fat tissue, which has rarely been documented. The histopathological and immunohistochemical results support a hypothesis about the pathogenesis of this neoplasm.

CASE PRESENTATION

Chief complaints

A 60-year-old Chinese man presented to the Department of Urology with a 5-year history of a cystic mass in the left kidney, the size of which had increased after his fall 2 mo ago.

History of present illness

The patient who was annually receiving medical examinations given by his employer was told in 2017 that he had a cystic mass in the left kidney. This lesion occurred as a painless mass, approximately 3 cm in the greatest diameter. He denied any obvious clinical symptoms except occasional mild distending feelings and soreness in the left loin. He fell 2 mo ago. A computed tomography (CT) scan of the abdomen at a local hospital showed a growing mass (measuring 6 cm in diameter) in the kidney.

History of past illness

The patient had suffered from hypertension for more than 10 years. He denied any typical symptoms of tuberous sclerosis such as facial sebaceous adenoma, epilepsy, or intellectual disability. There was no clinical imaging showing sporadic lymphangioleiomyomatosis like pneumothorax, chylous pleural effusions, or cystic lung disease. He denied any eye symptoms, heart disease, pulmonary abnormalities, or bone disease.

Personal and family history

The patient denied any family history of renal diseases, including renal masses, renal cell carcinoma (RCC), AML, and tuberous sclerosis.

Physical examination

On physical examination, the vital signs were as follows: Body temperature, 36.0 °C; blood pressure, 137/87 mmHg; heart rate, 73 beats per min; respiratory rate, 20 breaths per min. The physical examination revealed no abnormalities.

Laboratory examinations

Laboratory tests after admission were as follows: White blood cell count (3.36 × 10^9/L; normal range: 4.0-10.0), red blood cell count (3.41 × 10^{12}/L; normal range: 3.50-5.50), and platelet count (188 × 10^9/L; normal range: 90-300). The results of biochemistry tests were: Alanine aminotransferase (26 U/L; normal range: 0-40), aspartate aminotransferase (68 U/L; normal range: 0-40), total albumin (82.7 g/L; normal range: 64-82), glucose (6.24 mmol/L; normal range: 3.9-6.1), triglyceride (2.39 mmol/L; normal range: 0.4-1.8), and potassium (3.27 mmol/L; normal range: 3.5-5.1).

Imaging examinations

A CT scan at our hospital discovered an 8.6 cm × 7.4 cm, oval to round, mixed hypodense and isodense, cystic exophytic lesion with mainly liquid density in the middle-lower pole of the left kidney (Figure 1A). The left kidney was compressed and shifted upward. The lesion was well demarcated, encircled by an asymmetrical, irregular wall thickened in the areas adjacent to the renal parenchyma. Small mural nodules, a smooth linear septum, and an inconspicuous patch inside the lesion could be seen (Figure 1B). These features were slightly enhanced in the cortical phase and gradually washed out in the late phase (Figures 1C and D). The central liquid area remained unenhanced. There was no macroscopic fat density. The CT attenuation value varied from -8 Hounsfield units (HU) to 32 HU. Regional lymph node metastasis and intravascular extension were not observed.

FINAL DIAGNOSIS

Fat-poor RAML with prominent cystic degeneration.

TREATMENT

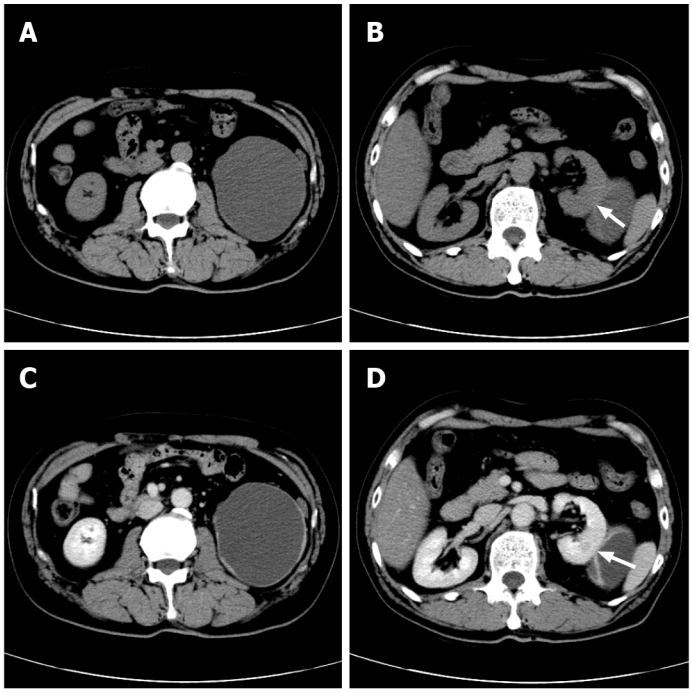
A laparoscopic unroofing operation for the renal cyst was initially performed. The wall of the cystic mass was broken during the operation, producing dull red liquid. The mass was clearly demarcated from the normal tissues with a capsule. A disordered form, visible errhysis, and coagula were found at the bottom of the mass, around which there was hemosiderosis. With concern for misdiagnosis of malignancy and bleeding risk with percutaneous biopsy, intraoperative frozen examination was performed. This was unable to rule out cystic RCC.

Finally, the patient underwent radical nephrectomy. The excised mass was fixed in formalin and embedded in paraffin. Hematoxylin and eosin staining and immunohistochemistry were performed to establish a definitive diagnosis. Pathologically, the remnant of the cystic lesion mainly consisted of tortuous, ectatic, and partly hyalinized blood vessels and mature adipose tissue, which were organized sporadically in a sheet-like pattern among the abnormal blood vessels (Figure 2A). The smooth muscle-like spindle cells, whose nuclei differed in size, were arranged randomly as short fascicles with a focal radial configuration. Hemorrhage, slight inflammatory cell infiltration, and inconspicuous necrotic foci were observed. Epithelioid cells were absent (Figure 2B).

Immunostaining showed that, in addition to neuron-specific enolase (Figure 3A), the tumor cells exhibited positivity for melanosome-associated proteins, including human melanoma black-45 (HMB-45) (Figure 3B) and Melan-A (Figure 3C), S-100 (Figure 3D), and smooth muscle proteins, including smooth muscle actin (SMA) (Figure 3E) and calponin (Figure 3F), which were strongly stained in the spindle cells. In contrast, staining for estrogen receptor (Figure 3G), progesterone receptor (Figure 3H), CD68 (Figure 3I), and cytokeratin (CK) (Figure 3J) was negative. The Ki-67 labeling index (Figure 3K) was less than 5%.

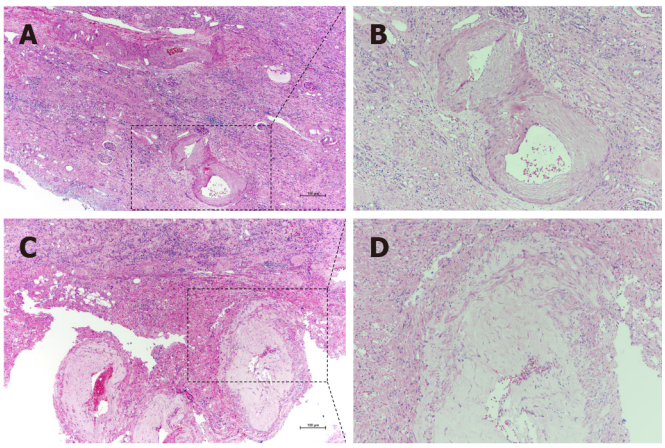
OUTCOME AND FOLLOW-UP

The patient underwent radical nephrectomy. No complications were noted during or after surgery. Electrocardiogram and chest X-ray examination were performed half a year after operation, and no



DOI: 10.12998/wjcc.v11.i2.417

Figure 1 Computed tomography of the kidney with cystic degeneration. A: Plain computed tomography (CT) revealed an 8.6 cm × 7.4 cm, oval to round, mixed hypodense and isodense, cystic exophytic lesion with mainly liquid density; B: A smooth linear septum was observed (arrow); C: Enhanced scan revealed enhancement of the nodules and irregular wall; D: The smooth linear septum (arrow).



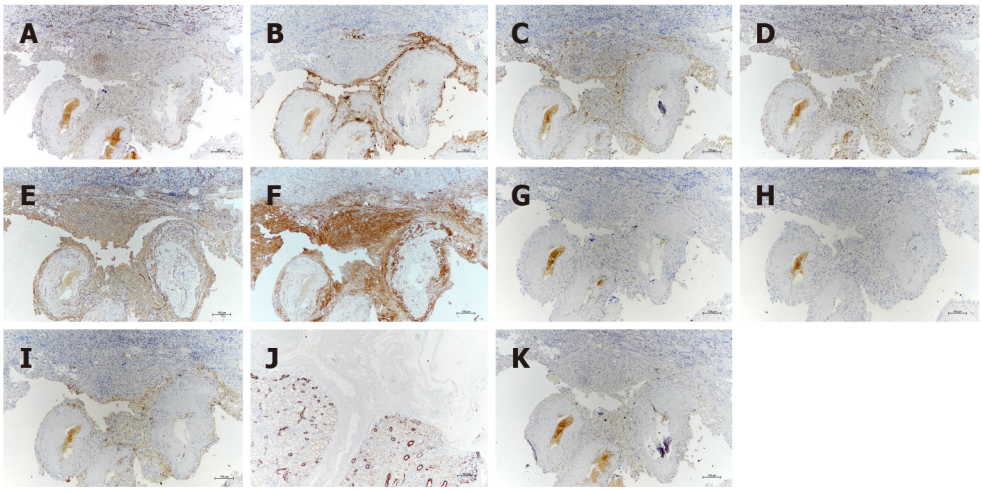
DOI: 10.12998/wjcc.v11.i2.417

Figure 2 Histopathological findings of renal angiomyolipoma with cystic degeneration. A: Hematoxylin and eosin staining showed tortuous and ectatic tumor vessels with uneven and thick wall in the critical renal parenchyma; B: Randomly arranged smooth muscle-like spindle cells with nuclei of different sizes. Original magnification × 200 and × 400 (insets).

obvious abnormality was found.

DISCUSSION

AML is a well-known tumor that is composed of dysmorphic blood vessels, smooth muscle, and mature adipose tissue in variable proportions. Immunohistochemically, positivity for HMB-45 and Melan-A, two melanocytic markers, is often observed in spindle tumor cells. Smooth muscle markers such as SMA are also positive. Meanwhile, the mass does not express CKs and other epithelial markers[2]. Imaging technology plays an important role in the AML diagnosis, with the significant identification of the macroscopic fat component, which appears as a homogeneous hyperechoic mass on B-mode ultrasound and results in the loss of signal intensity on fat suppression imaging. CT has excellent sensitivity, specificity, positive predictive value (PPV), and negative predictive value in identifying AML[4].



DOI: 10.12998/wjcc.v11.i2.417

Figure 3 Immunoprofile of renal angiomyolipoma with cystic degeneration. A-F: Tumor cells exhibited positivity for neuron-specific enolase (A), human melanoma black-45 (B), Melan-A (C), S-100 (D), smooth muscle actin (E), and calponin (F); G-J: They did not express estrogen receptor (G), progesterone receptor (H), CD68 (I), or cytokeratin (J); K: The Ki-67 labeling index was less than 5%. Original magnification × 200.

Histologically, classic RAML usually presents as a well-delineated, isodense and hypodense mixed renal cortical mass, containing various proportions of visible fat with attenuation < -10 HU on unenhanced CT (UECT) images. Thin-slice multidetector row CT[5] and double-echo gradient-echo chemical shift magnetic resonance imaging (MRI)[6] can be used to differentiate AML with minimal fat from other renal neoplasms. However, the imaging diagnosis of AML will become indeterminate in two situations. First, the fat component of "minimal-fat" or "fat-poor" AML (defined as fat cells < 25% per high-power field[7-9]) is invisible. Second, hemorrhage, necrosis, or cystic degeneration may obscure the underlying fat[10].

To our knowledge, AML with cystic degeneration has rarely been documented and only accounts for less than 1% of RAMLs. In addition, most cystic AMLs consist of multiple small cysts with or without grossly depicted large cysts[11]. In this case, we reported a patient with a cyst-prominent RAML containing little fat tissue and only one septum on UECT. Based on the clinical and laboratory data, we propose a possible pathophysiologic mechanism: Trauma from the patient's fall ruined the fragile vascular wall of the tumor and resulted in rupture. As hemorrhage occurred, the size of the tumor slowly increased. The patient did not suffer any serious clinical symptoms, perhaps owing to the cystic capsule, composed of tumor tissues and adjacent fibrous texture, which prevented the exudate from approaching the peritoneum. The central area of the tumor grew faster and was correspondingly lacking blood supply, thus resulting in local necrosis and liquefaction. Additionally, the poor blood supply was exaggerated with abnormal blood vessels, resulting in the enlargement of the necrotic region. Meanwhile, a part of the nephric tubules was likely physically compressed by the tumor tissues, leading to hydronephrosis and an increase in tumor size. The apparent synergy between bleeding, necrosis, liquefaction, and potential hydronephrosis supports the formation of an internal and fluid-filled prominent cystic mass with few residual lesions in the periphery. Over time, the degradation of blood and liquefied necrotic tumor produced the hypodensity on CT scan.

The absence of fat density, cystic appearance, and heterogeneous enhancement on contrast enhanced CT (CECT) raise a broad differential diagnosis, including cystic clear cell RCC, multilocular cystic RCC (MCRCC), papillary RCC (PRCC), oncocytomas, cystic nephroma (CN) or mixed epithelial and stromal tumors (MEST), and complex renal cysts. On ultrasound, the presence of an anechoic rim or intratumoral cysts suggests RCC, and shadowing suggests AML[12,13]. Doppler ultrasound also improves the ability to diagnose AML[14]. Cystic lesions of RCC generally display an irregular wall and are thicker than those of common cystic diseases. Compared with cystic RAML, the enhancement of mural nodules, septa, and solid composition in the cyst cavity of RCC is more obvious. Moreover, calcification is commonly found in RCC, but not in AML[15,16].

Homogeneous attenuation on UECT and enhancement on CECT images indicate that AML contains abundant muscle and minimal fat[7]. The early dark cortical band sign can be observed in up to 60% of clear cell RCC cases, facilitating the differential diagnosis from fat-poor AML with high specificity and PPV[17]. Some studies demonstrate that the combination of quantitative data obtained by specific region of interest in corticomedullary phase[18], convention-radiomics CT nomogram[19,20], and circularity index on CECT[21] help distinguish fat-poor AML from clear cell RCC. Magnetic resonance parameters may be of value in evaluating RCCs[5,22]. The immunoprofile of clear cell RCC is identical to other epithelial tumors which exhibit strong cytoplasmic expression of CK and epithelial membrane antigen[23,24].

Historically, MCRCC is considered to be a subtype of RCC[25]. The 2004 World Health Organization classification of kidney tumors categorized MCRCC as a separate entity with a good prognosis[26]. The diagnostic criteria for MCRCC include a grossly multilocular cystic appearance, a yellowish solid component limited to small areas with no expansive nodules and no tumor necrosis, and a microscopically low grade[27]. Hemorrhage, necrosis, and cystic degeneration are also common in PRCC and oncocytomas[26,28]. PRCC has variable proportions of papillae and may be bilateral or multifocal[26]. On imaging, PRCC is distinguished by the low level of enhancement and shows progressive enhancement when evaluated in the arterial (50-60 HU) and venous phases (65-75 HU)[24,29]. Meanwhile, PRCC is hypointense on T2-weighted images[5,24]. Oncocytomas display a central stellate scar that is hypodense on CT. The intense enhancement peaks in the nephrographic phase and rapidly washes out[30,31]. Sharing a similar presentation with MCRCC on imaging, CN is a benign neoplasm belonging to the family of MEST of the kidney, which usually shows multilocular, thick-walled cystic lesions with numerous thick, smooth, and contrast-enhanced septations[29]. MEST normally appears as well-margined, multifocal cystic masses with septa and nodular components on CT. Spindle cells resembling ovarian stroma as well as the epithelium lining the cystic structures are typical components of MEST[32,33]. Complex renal cysts are believed to undergo rupture, hemorrhage, or an acute infection. The features of MEST on CT include high attenuation values, the presence of thick or calcified walls, and septations with or without nodules[29].

After the diagnosis of RAML, treatments aimed at preserving renal function, relieving clinical symptoms, and reducing bleeding risk should be carried out. Active monitoring is often proposed as the preferred strategy for asymptomatic masses smaller than 4 cm in diameter[34]. Direct clinical interventions are employed for patients with RAML as follows: Those with clinical symptoms, the largest diameter is greater than 4 cm, those suspected of having malignant transformation, and women of childbearing age[34-36]. Emergency patients or cases with aneurysms larger than 5 cm, tuberous sclerosis complex (TSC)-associated AML, and who cannot insist on follow-up should also be included [35,37]. The tumor volume of sporadic AML and TSC-associated AML both increases with time, while the sporadic type is usually asymptomatic and relatively slow in growth[38]. Therefore, the imaging follow-up interval for RAML should be determined according to the clinical situation of the patient.

Transcatheter arterial embolization (TAE), which is capable of shrinking tumor, hemostasis, and protecting normal renal tissue, can be performed safely without permanent impairment[39,40]. TAE is recommended as a first-line choice for bleeding AML[41]. Surgical resection is still the most effective treatment for AML with operation indications, including suspicion of malignancy, symptoms, and a high risk of hemorrhage. Compared with nephrectomy, partial nephrectomy (PN) can better preserve renal function and reduce mortality. Currently, the treatment of RCC is more likely to preserve nephron, which is also applicable to the treatment of AML[42]. PN, whether open surgical, laparoscopic, or robotic assisted, has become a common surgical procedure[39]. Dong *et al*[43] reported an off-clamp retroperitoneoscopic tumor evacuation, which is feasible, safe, and effective for treating complex sporadic RAMLs.

Mammilian target of rapamycin (mTOR) inhibitors, such as sirolimus or everolimus, a new targeted drug, can be used to treat patients with TSC and sporadic AML. These medications result in tumor shrinkage *via* inhibition of the mTOR pathway and subsequent tumor cell proliferation. Low-dose everolimus maintenance therapy represents an effective and tolerated approach to achieve TSC-associated AML control[44-46].

We present a rare case of AML with cystic degeneration as the main imaging clue, which easily raises a complex differential diagnosis. The clinical data and histopathological results further support a new possible subtype for RAML and explicate the pathogenesis. However, more cases and insights into underlying molecular mechanisms are required to confirm this conclusion.

CONCLUSION

In general, imaging is able to diagnose AML given its typical appearance. It is advisable to combine imaging performance on ultrasonography, CT, and MRI when diagnosing AML. In this case, we describe an atypical presentation of AML. When faced with a large cystic mass of the kidney, diagnosis is more complicated with a broad differential beyond AML. As imaging features in this context lack specificity, an accurate diagnosis relies on pathological examination. Various proportions of the three classic components detected microscopically along with immunohistochemical staining can provide a confident diagnosis of AML. Considering the risk of hemorrhage, early diagnosis and suitable treatments are very important. In clinical work, routine pathological examination should be considered. Furthermore, percutaneous biopsy can be an option to avoid potentially unnecessary surgery[24].

FOOTNOTES

Author contributions: Lu SQ and Lv W carried pathological analyses and drafted the manuscript; Liu YJ analyzed the images; Deng H conceived of this study and drafted the manuscript; and all authors issued final approval for the version to be submitted.

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CASE REPORT

Perivascular epithelioid cell tumors of the liver misdiagnosed as hepatocellular carcinoma: Three case reports

Yan-Qi Kou, Yu-Ping Yang, Wei-Xiang Ye, Wei-Nan Yuan, Shen-Shen Du, Biao Nie

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): 0
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Abstract

BACKGROUND

Hepatic perivascular epithelioid cell neoplasms (PEComas) are rare. Diagnostic and treatment experience with hepatic PEComa remains insufficient.

CASE SUMMARY

Three hepatic PEComa cases are reported in this paper: One case of primary malignant hepatic PEComa, one case of benign hepatic PEComa, and one case of hepatic PEComa with an ovarian mature cystic teratoma. During preoperative imaging and pathological assessment of intraoperative frozen samples, patients were diagnosed with hepatocellular carcinoma (HCC), while postoperative pathology and immunohistochemistry subsequently revealed hepatic PEComa. Patients with hepatic PEComa which is misdiagnosed as HCC often require a wider surgical resection. It is easy to mistake them for distant metastases of hepatic PEComa and misdiagnosed as HCC, especially when it's combined with tumors in other organs. Three patients eventually underwent partial hepatectomy. After 1-4 years of follow-up, none of the patients experienced recurrence or metastases.

CONCLUSION

A clear preoperative diagnosis of hepatic PEComa can reduce the scope of resection and prevent unnecessary injuries during surgery.

Key Words: Perivascular epithelioid cell neoplasms; Hepatocellular carcinoma; Case report; Diagnoses; Coexistence

Core Tip: Herein, we present three cases of hepatic perivascular epithelioid cell neoplasms (PEComas): One case of primary malignant PEComa, one case of benign PEComa, and one case of PEComa with ovarian mature cystic teratoma. The first case of PEComa cooccurred with an ovarian mature cystic teratoma. All three cases were misdiagnosed as liver cancer before surgery. A high rate of misdiagnosis of hepatocellular carcinoma is noted among patients with PEComa. A clear preoperative diagnosis of hepatic PEComa is crucial before deciding on a treatment plan, especially with the extent of surgical treatment in hepatocellular carcinoma.

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INTRODUCTION

Perivascular epithelioid cell neoplasms (PEComas) are mesenchymal tumors with the histological and immunophenotypic characteristics of perivascular epithelioid cells. PEComas include multiple tumor types, including angiomyolipoma, lymphangioma, lymphangioleiomyomatosis, clear cell sugar tumors, and tumor types not otherwise specified[1]. Only a few cases of PEComa originating in the liver have been reported, and the majority of these cases are benign[2,3]. Malignant hepatic PEComa are extremely rare.

Hepatic PEComas are typically found during routine physicals. Most patients present with a painless mass, and only a handful of these patients experience epigastric pain from mass compression[4]. The diagnostic criteria for hepatic PEComa have not been unambiguously defined and validated to date[5,6]. Given the current lack of global diagnostic standards for imaging and laboratory sciences, it is easy to mistake primary hepatic PEComa for hepatocellular carcinoma (HCC). Nevertheless, necrosis, mitotic activity, pleomorphism, marked nuclear atypia, infiltrative growth, and large size suggest malignant biological behavior. Hematoxylin-eosin staining and positive immunohistochemical staining for human melanoma black 45 (HMB45) and Melan A are the primary diagnostic evidence for PEComas[1,7]. The clinical and therapeutic management of hepatic PEComa is controversial, but surgery appears to be the preferred treatment[8].

The following is a summary of our experience in diagnosing and treating three patients with hepatic PEComas. This study will help form clinical guidelines for hepatic PEComas.

CASE PRESENTATION

Chief complaints

Case 1: A 37-year-old man was admitted to the hospital with abdominal pain for 1 mo.

Case 2: A 70-year-old woman who was admitted due to an asymptomatic hepatic mass for more than half a month.

Case 3: A 30-year-old woman was admitted to hospital with abdominal bloating for 6 mo.

History of present illness

Case 1: A nodular mass was discovered during an assessment of abdominal pain in the right lobe of his liver at another hospital.

Case 2: The asymptomatic hepatic mass was found during a routine physical examination at another hospital a half a month ago.

Case 3: A liver tumor accompanied by an ovarian lesion was discovered during a routine physical examination 16 d ago.

History of past illness

Case 1: The patient had been suffering from nonalcoholic fatty liver disease for over ten years.

Case 2: The patient claimed no history of past illness.

Case 3: The patient claimed no history of past illness.

Personal and family history
None of the three patients had any relevant personal or family history.

Physical examination
Physical examination of all three patients revealed no abnormalities.

Laboratory examinations
Case 1: Laboratory studies of liver function were standard, viral hepatitis markers and tumor indicators, such as alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA), carbohydrate antigen 199 (CA-199), and carbohydrate antigen 125 (CA-125), were all negative.

Case 2: Routine blood analysis, liver function, hepatitis virus, and specific tumor markers (including AFP, CEA, CA-125, and CA-199) were all normal.

Case 3: The serum tumor markers (AFP, CEA, CA-199) and serology for hepatitis B and C, but not CA-125, were all normal. Tumors of ovarian origin may account for the elevated CA-125 levels.

Imaging examinations
Case 1: Ultrasonography (US) revealed a hypoechoic, irregularly shaped nodule located in the right posterior lobe of the liver. Computed tomography (CT) with 3-phase enhancement of the upper abdomen was performed. The pre contrast CT scan exhibited a flake blur and a low-density shadow in S6 of the liver in the same location noted in the US. In contrast, the lesion is markedly enhanced in the arterial phase of contrast-enhanced CT scans. Gadolinium ethoxybenzyldiethylenetriaminepentaacetic acid-enhanced magnetic resonance imaging (MRI) is the liver-specific contrast enhancement agent currently used for the diagnosis of HCC. This assessment revealed a nodular abnormal signal shadow in S6 of the liver measuring 2.5 cm × 2.0 cm × 2.3 cm with smooth edges and a clear boundary. The lesion presented as hypointensity on T1-weighted images (T1WIs) and heterogeneous hyperintensity on T2-weighted images (T2WIs). The arterial phase revealed significantly enhanced lesions, whereas the portal venous phase exhibited a lower degree of enhancement compared with the liver parenchyma (Figure 1A and B). Based on the imaging findings, we suggested that the lesion was an HCC nodule.

Case 2: The woman presented with an ill-defined mass on US that was internally hypoechoic with a partial hyperechoic area. MRI exhibited a lesion with irregular edges and unclear boundaries that was approximately 5.0 cm × 3.0 cm × 3.1 cm in size located between the hepatic S3 and S4 segments. The lesion showed slight hypointensity on T1WI and heterogeneous hyperintensity on T2WI. In the arterial phase, the lesions displayed obvious heterogeneous enhancement. The enhancement of lesions was significantly weakened in the venous phase, and the neoplasm decayed to a low-signal state in the delayed phase (Figure 1C and D). Based on the imaging findings, the lesion appears to be an HCC nodule.

Case 3: US revealed a slightly heterogeneous hypoechoic nodule in the right anterior lobe of the liver. In a plain CT scan, the lesion (approximately 5.6 cm × 4.7 cm × 5.0 cm) exhibited an undefined mass with heterogeneous density in segment 8 of the liver. On arterial CT, the liver lesion was obviously heterogeneously enhanced. In the portal venous phase, the lesion rapidly returned to an isoattenuating state. Lesion enhancement in the portal and delayed phases decreased rapidly, and the strengthening method showed a rapid in and out pattern. MRI of the abdomen showed heterogeneous hypointensity on T1WI and hyperintensity on T2WI. In enhanced scanning, the lesion showed asymmetrical enhancement in the arterial phase images, and lesion enhancement was significantly weakened in the portal and delayed phase images (Figure 1E and F). Preoperative plain abdominal CT showed a right ovarian lesion measuring approximately 7.8 cm × 4.8 cm × 7.9 cm with multiple cystic low-density shadows scattered throughout. The boundaries of the lesion were clearly defined, and the lesion was not strengthened after undergoing contrast-enhanced computed tomography, which contained some fatty components (Figure 1G and H). According to the imaging findings, the liver lesion appears to be an HCC nodule, and the ovarian lesion is considered to be an ovarian tumor.

Pathological examination
Case 1: Based on intraoperative frozen pathological consultation, HCC was considered to be the most likely diagnosis. Ultimately, the patient underwent partial hepatectomy. Histopathologic results suggest that the tumor tissue is arranged in nests and sheets with rich, slender vascular networks connecting them. Tumor cells are similar in size but irregular in shape. The nucleolus is conspicuous in tumor cells. In addition, the nuclei were irregularly shaped (Figure 2A). Immunohistochemical staining studies showed that some tumor markers were negative, such as hepatocytes, Glypican-3 (GPC-3), cluster of

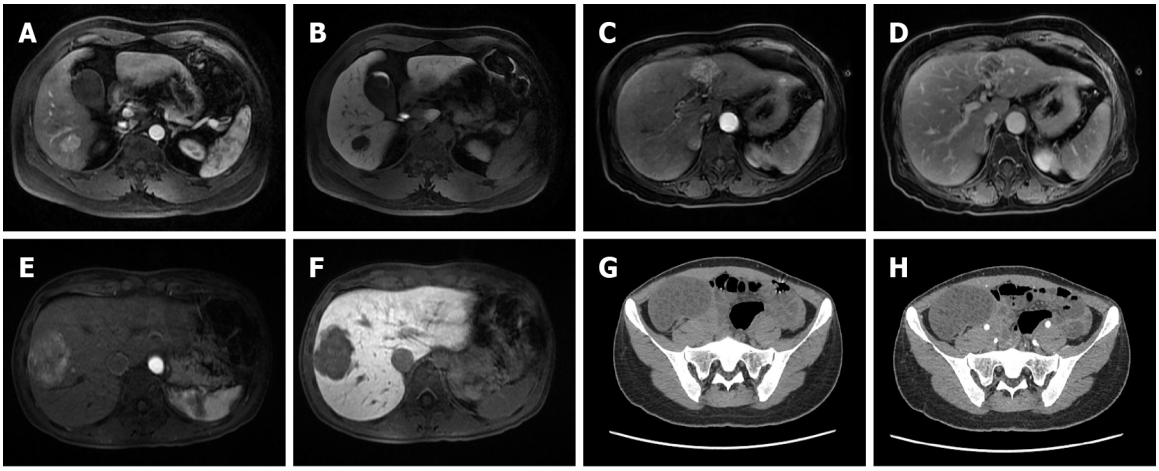

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Figure 1 Three cases misdiagnosed as hepatocellular carcinoma based on imaging findings. A and B: Case 1: Magnetic resonance imaging (MRI) of hepatic perivascular epithelioid cell neoplasms (PEComa) in a 37-year-old man: the lesion located in S6 showed distinct enhancement during the hepatic arterial phase (A), rim enhancement on the delayed phase (B); C and D: Case 2: MRI of hepatic PEComa in a 70-year-old woman, the lesion displayed obvious heterogeneous enhancement in the arterial phase (C), that was significantly weakened in the venous phase (D); E and F: Case 3: MRI of hepatic PEComa in a 30-year-old woman accompanied by an ovarian mature cystic teratoma: the lesions showed asymmetrical enhancement in arterial phase images in enhanced scanning (E), lesion enhancement was significantly weakened in the portal phase (F); G and H: preoperative plain abdominal computed tomography showed a right ovarian lesion with multiple cystic low-density shadows scattered throughout (G), the lesion was not strengthened after undergoing contrast-enhanced computed tomography (H).

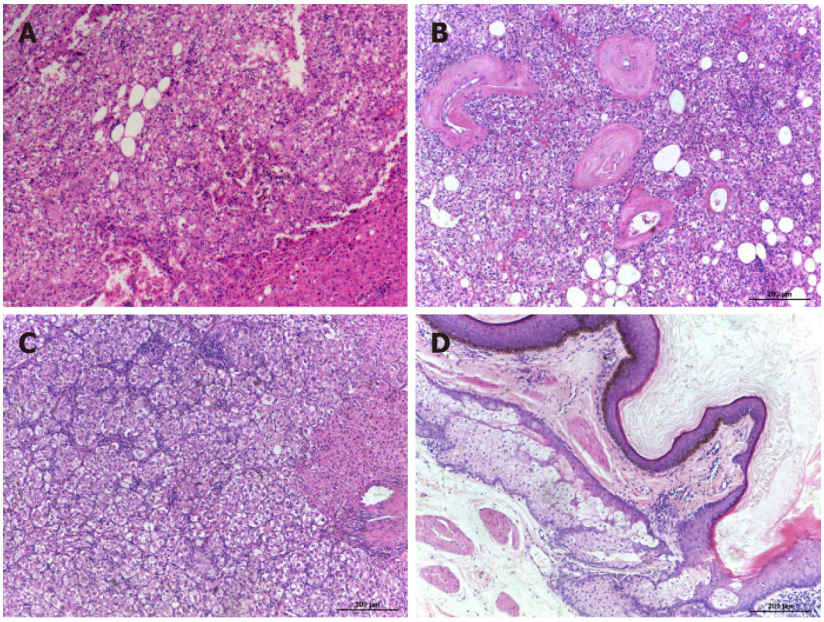

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Figure 2 Results of hematoxylin-eosin staining. A: Hematoxylin-eosin (HE) staining of the liver in case 1, a 37-year-old man; B: HE staining of the liver in case 2, a 70-year-old woman; C: HE staining of the liver in case 3, a 30-year-old woman; D: HE staining of the ovarian mature cystic teratoma in case 3, a 30-year-old woman.

differentiation (CD) 10, and AFP, while others were positive, such as CD34, Melan A and HMB45 (Figure 3A and D). The Ki-67 Labeling index was 10%.

Case 2: Histopathological results revealed that the tumor tissue formed nests and sheets connected by slender, rich vascular networks. Tumor cells were polygonal or round in shape and uniform in size. The nucleolus is conspicuous in tumor cells, and their nucleus is shaped regularly (Figure 2B). The tumor was positive for HMB45, Melan A and CD34 markers with a Ki-67 Labeling index of 1% (Figure 3B and E).

Case 3: Frozen pathological consultation conducted intraoperatively indicated the presence of HCC. The woman underwent surgery as a result of her condition. Histologically, the tumor comprises nests and

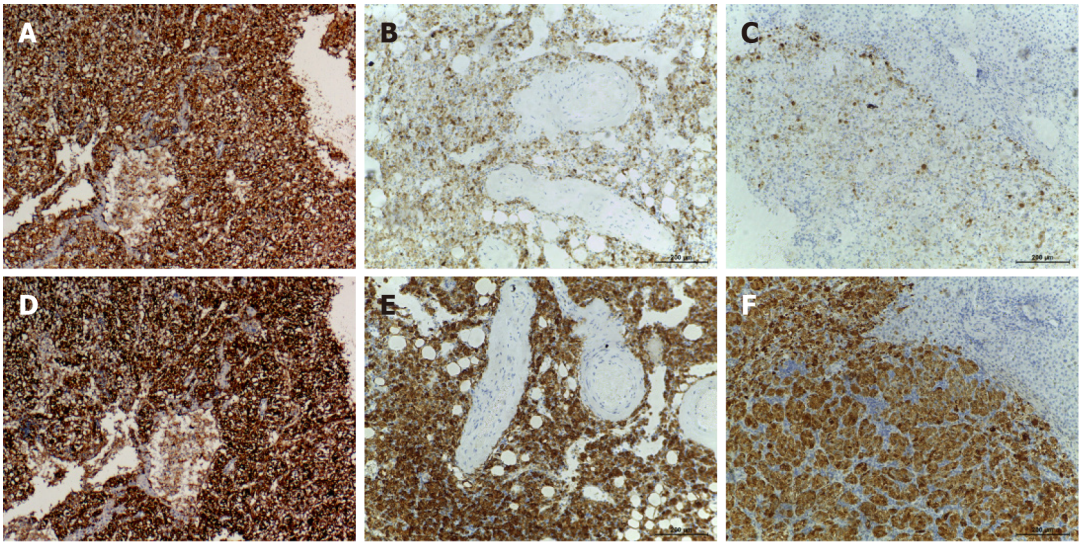

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Figure 3 Immunohistochemical staining results indicated that all three patients had hepatic perivascular epithelioid cell neoplasm. A: Positive staining for the biomarker human melanoma black 45 (HMB45) of case 1; B: Positive staining for HMB45 of case 2; C: Positive staining for HMB45 of case 3; D: Positive straining for the biomarker Melan A of case 1; E: Positive straining for Melan A of case 2; F: Positive straining for Melan A of case 3.

sheets of large, round to polygonal cells separated by a sinusoidal vascular network with hemorrhage areas. With distinct cell borders, the cells showed abundant cytoplasm, ranging from granular eosinophilia to clear cytoplasm. In tumor cells, the nucleolus is conspicuous, and its shape is regular. Mitoses was rare to absent (Figure 2C). Immunohistochemical analysis showed strong and diffuse expression of HMB45 and Melan-A, whereas markers for hepatocytes, GPC-3, and AFP were negative. The Ki-67 Labeling index was 5% (Figure 3C and F). Histopathologic examination of the ovarian lesion of the 30-year-old woman revealed that it was an ovarian mature cystic teratoma (Figure 2D).

FINAL DIAGNOSIS

Case 1: A malignant hepatic PEComa was eventually diagnosed based on morphological and immunohistochemical findings.

Case 2: Histopathology and immunohistology revealed that this tumor was a benign hepatic PEComa.

Case 3: Morphologic and immunohistochemical findings suggested the diagnosis of hepatic PEComa and an ovarian mature cystic teratoma was diagnosed by histopathology of the ovarian lesion.

TREATMENT

Case 1: The patient underwent partial hepatectomy.

Case 2: Ultimately, she underwent partial hepatectomy.

Case 3: She underwent partial hepatectomy and ovarian teratoma resection.

OUTCOME AND FOLLOW-UP

Case 1: After partial hepatectomy, the patient recovered and was discharged after 1 wk of postoperative care. The patient did not receive any adjuvant neoadjuvant therapy and has remained alive for 12 mo without recurrence or metastases.

Case 2: For the past 35 mo, the patient has not experienced recurrence or metastasis.

Case 3: The patient recovered well and after 46 mo of follow-up without recurrence or metastases.

DISCUSSION

In these three patients, it was challenging to differentiate between HCC and liver PEComa. Most patients with PEComa of the liver do not exhibit characteristic clinical symptoms, and a small number of patients may suffer from abdominal pain or abdominal discomfort[9]. Hepatic PEComas do not exhibit specific clinical or imaging characteristics, and preoperative imaging and intraoperative frozen pathological examinations as well as uncertainty regarding the optimal surgical margin may lead to misdiagnosis as a primary or metastatic HCC prior to surgery. As a result, the scope of liver resection is further expanded; thus, the minimal level of liver resection required for the trabecular pattern is not achieved.

The differential diagnosis of tumors as hepatic PEComa requires further discussion. PEComas in the liver are typically composed of mature adipose tissues surrounded by thick or thin walls of blood vessels. Epithelioid tumor cells are arranged radially around the vessels, exhibit different degrees of differentiation and are difficult to diagnose histologically[10]. When considering HCC, the significant epithelioid morphology and the trabecular pattern of hepatic PEComa make it extremely easy to misdiagnose it as HCC, particularly based on intraoperative frozen pathological diagnosis. Hepatic PEComa was incorrectly identified as HCC based on frozen pathological analysis in the present cases. Due to morphological similarities, epithelioid tumors, such as HCC, can be easily confused with hepatic PEComa. Thus, it can be challenging to achieve a surgical frozen pathological diagnosis within a short period of time, leading to a high misdiagnosis rate[11,12].

Furthermore, the imaging characteristics of this tumor are related to the histological components; in particular, most tumors are completely devoid of adipose tissue, so fat attenuation is rarely observed on computed tomography and magnetic resonance images[13]. In contrast, the appearance of a hepatic PEComa on CT or MRI is well defined with early enhancement in the arterial phase and nonuniform enhancement in the venous and delayed phases[14]. Lesions with delayed washout may mimic HCC [15]. Consistent with the study results, hepatic PEComa should still be considered whenever a blotchy vascular pattern of the tumor is noted, if there is no evidence of hemorrhage in the tumor, if there is no abnormality in the background parenchyma, when no hepatitis virus markers have been detected, and when liver function tests and tumor markers (AFP, CEA) are normal[16]. Nevertheless, elevated AFP is present in a few cases[17].

Although patients completed US, tomography with three-phase enhancement, enhanced MRI tests and intraoperative frozen pathology, these results suggested HCC nodules until the postoperative pathology and immunohistochemistry confirmed the lesions as primary hepatic PEComas. Its postoperative pathological characteristics include a nest-like arrangement of tumor tissue and a thin vascular network that shuttles between cells. The observation of large clear cells or large cells with eosinophilic condensation around the nucleus alerts the pathologists to the possibility of a PEComa. Importantly, immunohistochemical staining studies confirmed that the lesion is negative for the hepatocyte marker and positive for the specific immunomarkers HMB-45 and Melan-A[18].

To diagnose hepatic PEComa, ultrasound imaging showed clear and specific imaging manifestations of the lesions in the patients. Contrast-enhanced ultrasound (CEUS) could be valuable in differentiating hepatic PEComa from HCC. Hepatic PEComa lesions exhibit a significantly delayed washout compared with other malignant tumors, such as HCC and metastatic liver cancer. Color Doppler flow imaging demonstrated that the larger blood vessels surrounding the lesion may also represent a potential feature of hepatic PEComa[19,20]. Using Sonazoid® contrast agent in CUES may assist in the diagnosis of hepatic PEComa[21]. A mono-typical epithelioid variant of typical hepatic PEComa has been described with some cases exhibiting a pure sinusoidal trabecular pattern that mimics the characteristics of HCC. A pathologist should be familiar with the cytomorphology of hepatic PEComa and its tendency to mimic HCC. If characteristic cell morphologic features or clinical background are not observed, immunostaining of fine needle aspiration cytology or core biopsy must be performed to prevent misdiagnosis[22].

CONCLUSION

PEComa of the liver is a rare disease with a high probability of misdiagnosis. CEUS may contribute to a more confirmative differential diagnosis of hepatic PEComa. Additionally, immunohistochemistry is currently the only clinical method available to confirm the diagnosis, and surgery is the primary treatment. A clear preoperative diagnosis of hepatic PEComa is essential to determine the extent of surgery that should be performed.

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FOOTNOTES

Author contributions: Kou YQ, Yang YP, and Ye WX contributed equally to this manuscript and can be regarded as co-first authors; Nie B and Kou YQ contributed to the conceptualization and methodology; Yang YP, Ye WX, and Kou YQ contributed to the visualization and investigation; Ye WX, Yuan WN and Du SS contributed to the data curation; Yang YP and Kou YQ contributed to the writing and original draft preparation.

Informed consent statement: Informed written consent was obtained from the patient for publication of this report and any accompanying images.

Conflict-of-interest statement: The authors declare that they have no conflict of interest.

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CASE REPORT

H7N9 avian influenza with first manifestation of occipital neuralgia: A case report

Jie Zhang

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Peer-review model: Single blind

Peer-review report's scientific quality classification

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Abstract

BACKGROUND

Most of the first symptoms of avian influenza are respiratory symptoms, and cases with occipital neuralgia as the first manifestation are rarely reported.

CASE SUMMARY

A middle-aged patient complaining of paroxysmal pain behind the ear was admitted to our hospital. The patient's condition changed rapidly, and high fever, unexpected respiratory failure, and multiple organ failure developed rapidly. The patient was diagnosed with H7N9 avian influenza based on etiology.

CONCLUSION

We believe that the etiology of occipital neuralgia is complex and could be the earliest manifestation of severe diseases. The possibility of an infectious disease should be considered when occipital neuralgia is accompanied by fever. Avian influenza is one of these causative agents.

Key Words: Occipital neuralgia; Avian influenza; Respiratory; Infectious; Case report

Core Tip: Patients with avian influenza usually first show respiratory symptoms, and occipital neuralgia caused by avian influenza is very rare. We report a case of severe avian influenza pneumonia with occipital neuralgia as the first symptom.

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INTRODUCTION

Most of the first symptoms of avian influenza are respiratory symptoms, and cases with occipital neuralgia as the first manifestation are rarely reported. In June 2017, a middle-aged patient complaining of paroxysmal pain behind the ear was admitted to our hospital. The patient's condition changed rapidly, and high fever, unexpected respiratory failure, and multiple organ failure appeared rapidly. The patient was diagnosed with H7N9 avian influenza by etiology. This case is described as follows.

CASE PRESENTATION

Chief complaints

A 57-year-old male presented with sudden right postauricular tingling for 3 d (onset June 10th).

History of present illness

A 57-year-old male presented with sudden right postauricular tingling for 3 d (onset June 10th). The patient experienced discharge-like pain in the right postauricular region for a few minutes each time, lasting several seconds at a time. The pain was intense and severely affected the patient's life. No obvious nausea, vomiting, cough, diarrhea, limb weakness, or fever was observed.

History of past illness

There was no special history of past illness.

Personal and family history

No special personal and family history.

Physical examination

Physical examination results were normal. Nervous system examination showed that the right postauricular occipital nerve distribution area had acupuncture-induced hypersensitivity, whereas the rest of the nervous system examination showed no abnormalities.

Laboratory examinations

Routine blood analysis showed (June 13th) that the percentage of neutrophils was 84.6%, and the other blood biochemical indicators were generally normal: Erythrocyte sedimentation rate (ESR), 25 mm/h, sodium: 131.0 mmol/L. Coagulation tests, thyroid function tests (FT3, FT4, TSH, TG-Ab, and TPO-Ab), and liver and kidney function tests were normal. Antistreptolysin O (ASO), rapid detection of infectious diseases, and urine analysis showed no abnormalities. Stool analysis, glycosylated hemoglobin, and serum homocysteine levels were normal. The current perception threshold (CPT) indicated that the right lesser occipital nerve was hypersensitive (with small fibers involved, Table 1). See Tables 2-4 for Biochemical parameters of blood results, blood coagulation function results and Aterial blood gases results of patient. The patient had two chest X-ray examinations, the results were shown in Figure 1. The nucleic acid polymerase chain reaction (PCR) for influenza H7N9 virus in sputum specimens was positive at Chaoyang Hospital on the same day. The specimens sent to the Beijing Center for Disease Control and Prevention (CDC) and the Chinese National Influenza Center (CNIC) tested positive for H7N9 virus.

Imaging examinations

Head magnetic resonance imaging is normal. Fever occurred in the afternoon of the same day after admission. The patient had a temperature of 39.2 °C and cough that night. Pulmonary computed tomography (CT) (June 14th) showed inflammation in the right lower lung, fine moist rales in the right lower lung, and normal oxygen saturation. The patient's condition changed rapidly, and high fever, unexpected respiratory failure, and multiple organ failure. Chest X-ray re-examination showed that bilateral lung infection was significantly worse than yesterday's chest film (Figure 1).

FINAL DIAGNOSIS

The patient was finally diagnosed with H7N9 avian influenza by etiology.

Table 1 Current perception threshold examination of the occipital nerve

Nerve	Left/Right	2000 Hz (40/244/118)	250 Hz (4/52/19)	5 Hz (1/38/10)
Lesser occipital nerve	L	210	32	30
	R	200	60	80
Greater occipital nerve	L	220	52	30
	R	220	50	36
Greater auricular nerve	L	160	48	30
	R	150	45	26

The minimum/maximum/mean value of current perception threshold in normal people is shown in brackets. L: Left; R: Right.

TREATMENT

Fever occurred in the afternoon of the same day after admission. The patient had a temperature of 39.2 °C and cough that night. Routine blood analysis showed (June 13th) that the percentage of neutrophils was 84.6%, and the other blood biochemical indicators were generally normal: ESR, 25 mm/h, sodium: 131.0 mmol/L. Coagulation tests, thyroid function tests (FT3, FT4, TSH, TG-Ab, and TPO-Ab), and liver and kidney function tests were normal. ASO, rapid detection of infectious diseases, and urine analysis showed no abnormalities. Stool analysis, glycosylated hemoglobin, and serum homocysteine levels were normal. The CPT indicated that the right lesser occipital nerve was hypersensitive (with small fibers involved, Form 1). The patient's headache was relieved after 0.3 g oxcarbazepine. The patient still had persistent moderate to high fever, cough and sputum, pharyngeal pain, and yellow phlegm with blood filaments. Pulmonary CT (June 14th) showed inflammation in the right lower lung, fine moist rales in the right lower lung, and normal oxygen saturation. An intravenous drip of ceftazidime and levofloxacin was administered to the patient. The consultant of the Respiratory Department considered pneumonia and allowed him to be transferred to the department for further treatment (12:00 am on June 15th). On the day of transfer to the Respiratory Department, the patient experienced bad wheezing and dyspnea. Electrocardiogram (ECG) monitoring indicated that oxygenation decreased to 50% (oxygen flow, 10 L/min). Examination revealed widely flooded bubbles in both lungs. The patient had a body temperature of 39.5 °C. Cyanosis of the lip and spots on the trunk and lower extremities were also visible. The patient was administered lysine aspirin (0.45 mg), static push, and noninvasive ventilator-assisted ventilation treatment with the following parameters: S mode, IPAP 14 cm H2O, and EPAP 4 cm H2O. Oxygenation increased to 80%, and dyspnea did not improve. The respiratory frequency was 40 breaths/min, and the ventilator parameters were adjusted to ST mode, IPAP 16 cmH2O, and EPAP 5.0 cm H2O. The patient was given "imipenem combined with moxifloxacin" as anti-infection and nasal-fed "oseltamivir" as antiviral treatment. ECG monitoring at 12:45 pm revealed that the heart rate increased to 190 beats/min, and the blood oxygen level continued to 80%. Chest X-ray re-examination showed that the bilateral lung infection was significantly worse than Yesterday's chest film (Figure 1). With the consent of the family members, the patient was administered propofol sedation and tracheal intubation. After intubation, hemorrhagic secretions from the oral cavity and tracheal cannula were intermittently gushed in large quantities, and the patient was treated with an invasive ventilator. Acute bedside echocardiography findings showed reduced left ventricular systolic and diastolic functions (EF, 36%). The patient was successively administered tolasemide (40 mg) and morphine (5 mg) to reduce oxygen consumption. Rapid blood gas analysis at 13:37 pm showed the following results: pH 7.08, PO2 60 mmHg, and PCO2 55 mmHg. Slow vein input of 250 mL of sodium bicarbonate as a corrective treatment was administered considering metabolic acidosis. Concentrated salt supplementation was administered because the patient had low chlorine and sodium levels. After the treatment, the patient's heart rate gradually decreased to normal, but the whole body was damp and cold. The patient was treated with noradrenaline and vasoactive dopamine drugs to prevent hypotension. The patient was agitated and sedated using propofol and midazolam. He was transferred to the intensive care unit (ICU) for further treatment (19:00 on June 15th) considering acute respiratory distress syndrome (ARDS) with severe pneumonia, respiratory failure, metabolic acidosis, and cardiac insufficiency. After transfer to the ICU, ventilator-assisted ventilation was immediately connected and the patient's oxygenation status was difficult to maintain. When transferring the patient to the ICU, physical examination and drug sedation were performed. The patient had a blood pressure of 136/71 mmHg and was administered dopamine and norepinephrine. The patient also had an oxygen saturation of 80%, multiple moist rales in both lungs, a heart rate of 130 beats/min, rhythm, strong heart sounds, abdominal softness, and borborygmus (four times/minute), but his limbs were not swollen. Laboratory examination showed influenza A virus antigen (-), TB-IgM, TB-IgG (-), and PCT 0.77. Blood culture showed no bacterial growth. D-dimer 23.55 mg/L, OB (+). Liver function, renal function, myocardial enzyme levels, and

Table 2 Biochemical parameters of blood

Time	Routine blood test					Liver function						Renal function		Blood electrolytes			Cardiac function		
	WBC (10^9/L)	NEUT (%)	RBC (10^{12}/L)	HGB (g/L)	PLT (10^9/L)	ALT (U/L)	AST (U/L)	LDH (U/L)	GGT (U/L)	AMY (U/L)	CK (U/L)	CREA (umol/L)	UREA (mmol/L)	K (mmol/L)	Na (mmol/L)	CL (mmol/L)	BNP (pg/mL)	TNI (pg/mL)	CK-MB (ng/mL)
6.13	6.2	87.8	4.84	149	165							67	4.12	3.74	139	99.1			
6.14	4.8	84.6	4.62	144	144	25.2	38.2	332.8	155.6	34.1	237.4	62.6	3.83	4.03	131	94.7			9.2
6.15AM	4.1	76.1	5.17	159	119		220	4392			10254	62	5.75	4.46	123	93.2	1028	70.65	15.22
6.15PM	10.1	82.8	5.66	175	138	89.7	543	4926	161	440	11209	153	9.46	4.65	116	95.6			117

WBC: White blood cell count; NEUT: Neutrophil ratio; BBC: Red blood cell count; HGB: Hemoglobin; PLT: Platelet; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; LDH: Lactate dehydrogenase; GGT: γ-glutamyl transpeptidase; AMY: Amylase; CK: Creatine kinase; CREA: Creatinine; UREA: Urine creatinine; K: Kalium; Na: Sodium; CL: Chlorine; BNP: B-type natriuretic peptide; TNI: Troponin I; CK-MB: Creatine kinase isoenzyme-MB.

coagulation functions were significantly abnormal. The examination results since admission were as follows (Charts 1–3). The illness was interpreted by family members. The patient had acute onset of the disease, which progressed rapidly. The patient had sepsis with ARDS, respiratory failure, and heart, liver, and kidney function damage and was in a critical condition. Vancomycin+biapenem+ azithromycin+tami was administered for antimicrobial treatment against G+ and G bacteria as well as viral and atypical pathogens. The patient's blood oxygen level under invasive ventilation was still difficult to maintain at a normal level. Bedside veno-venous extracorporeal membrane oxygenation (ECMO) treatment (2:00 am on June 16th) was initiated, and the blood oxygen saturation increased to approximately 95%. After receiving ECMO, the patient's blood pressure dropped, and he was transfused with 2 U of suspended red blood cell type A and 400 mL of plasma. The patient was transferred to the respiratory ICU (RICU) of Chaoyang Hospital of Beijing (5:00 am on June 16th). The nucleic acid PCR for influenza H7N9 virus in sputum specimens was positive at Chaoyang Hospital on the same day. The specimens sent to the Beijing CDC and the CNIC tested positive for H7N9 virus. The final diagnosis was H7N9 avian influenza virus pneumonia. The patient was not asked about the relevant epidemiological contact history from the beginning to the end of the study. The patient remained in the RICU of Chaoyang Hospital and was subjected to actively supported treatment.

OUTCOME AND FOLLOW-UP

The patient's condition gradually stabilized. After 2 mo, the patient recovered and went home.

Table 3 Coagulation function

Time	PT (S)	PT (%)	INR	APTT (S)	FIB (mg/dL)	TT (S)
6.14	12.9	82.4	1.12	39.7	607.5	16.5
6.15	16	50.4	1.39	67.8	344.6	20.9

PT: Prothrombin time; PT%: Prothrombin activity; INR: International normalized ratio; APTT: Activated partial thromboplastin time; FIB: Fibrinogen; TT: Thrombin time.

Table 4 Aterial blood gases

Time	PH	PO2 (mmHg)	PCO2 (mmHg)	Lac (mmol/L)	SO2 (%)	BE (mmol/L)	cHCO3 (mmol/L)	A-aDO2 (mmHg)	%FiO2 (L)
6.15 11:25 am	7.32	36	37	2.1	56	-5.9	19.1	210	41
6.15 13:37pm	7.08	60	55	4.9	69	-14	16.5	584	100
6.15 15:21pm	7.18	56	50	3	75	-9.8	16.5	595	100

PH: Blood acid-base scale; PO2: Partial pressure of oxygen; PCO2: Arteriovenous carbon dioxide partial pressure difference; Lac: lactic acid; SO2: Oxygen saturation; BE: Base excess; cHCO3: Concentration of bicarbonate in plasma; A-aDO2: Alveolar-arterial oxygen difference; %FiO2: Fraction of inspired O2.

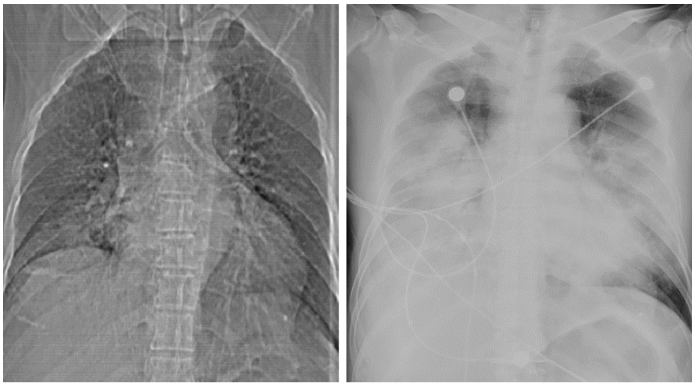

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Figure 1 Chest X-ray re-examination showed that bilateral lung infection was significantly worse than yesterday's chest film.

DISCUSSION

The patient who was subjected to a thrilling rescue process eventually developed avian influenza. The most important finding was that the first symptom was occipital neuralgia. According to the literature, no relevant reports are available on avian influenza with occipital neuralgia. Occipital neuralgia is described as paroxysmal pain in the major distribution of the greater occipital nerves or lesser occipital nerves (LON). Ten percent of cases are due to LON[1-5]. Occipital neuralgia is paroxysmal, lasting seconds to minutes, and often consists of lancinating pain that directly results from the pathology of one of these nerves. The occipital nerve is separated from the anterior branch of the second cervical nerve through the superficial cervical plexus, and ascends around the posterior margin of the sternocleidomastoid muscle. The distribution is in the mastoid process and posterior auricular region. Lower occipital neuralgia is a common type of neuralgia. The incidence of lesser occipital neuralgia is second only to that of great occipital neuralgia. The diagnostic criteria for lesser occipital neuralgia are unilateral or bilateral pain that meets the following criteria: (1) Pain is distributed in the small occipital nerve; (2) Pain has two of the following three characteristics: recurrent paroxysmal or persistent pain for several seconds to minutes; B - severe pain; C - sudden, penetrating, intense pain; and (3) Other diagnoses cannot be explained better.

The patient was diagnosed with lesser occipital neuralgia. Quantitative sensory analysis at the time of onset also indicated sensory hypersensitivity in the area of the lesser occipital nerve distribution (small fiber involvement). The effect of oxcarbazepine significantly supports this diagnosis. Occipital neuralgia can be classified into primary and secondary causes. Primary occipital neuralgia has fewer diseases,

most of which are secondary to nerve damage. The anatomical structure of the occipital nerve leads to a high incidence of occipital neuropathy because the greater occipital nerve and lesser occipital nerve have to travel a considerable distance between muscles, tendons, and blood vessels after leaving the osseous structure to finally reach their respective dominant skin areas. The occipital nerve may be involved in this process, and pain may occur in any adjacent structure[6]. According to different secondary causes of occipital neuralgia, the disease can be divided into occipital muscle structure abnormalities, occipital bone structure abnormalities, occipital vascular structure abnormalities, occipital nerve structure abnormalities, and occipital suspension structure abnormalities[1,7-9]. For example, compression and deformities occur in the C2 region[1,10]. Cervical spondylotic radiculopathy is the most common cause of compression[11]. In addition, intramedullary lesions of the high cervical spinal cord can cause occipital neuralgia and even pressure on the helmet[12,13]. Abnormalities in occipital suspension structures have gained increasing attention[14]. The occipital nerve is enclosed by two layers of connective tissue lumen attached to the nerve intima. The fluid in the lumen is balanced by nutrient vessels and the absorption of arteries, the venous plexus, and nerves to avoid occipital nerve compression. The outer space is located in the epineurium. The connective tissue lumen is interdependent with other structures, such as the perineurium, subperineural space, nerve intima, and glia, which form local pressure. Suspension reticular structures can protect the occipital nerve and are vulnerable to the influence of adjacent structures or the external environment. Neck muscle strain, cold weather, ischemia, or cold fatigue can destroy the balance of the suspension network, increase intracavity pressure, and cause occipital nerve pain.

Our case of H7N9 avian influenza with severe occipital neuralgia as the first symptom is rare in the clinical setting. No relevant reports have been found in the literature at home and abroad. A case of occipital neuralgia caused by a herpes zoster virus infection has been reported[15]. The pathogenesis may be related to abnormal occipital suspension structure caused by respiratory virus infection. In addition, the lesser occipital nerve is separated from the anterior branch of the second cervical nerve through the superficial cervical plexus, bypassing the upward margin of the sternocleidomastoid muscle. The superficial cervical plexus is located in the deep part of the sternocleidomastoid muscle behind the carotid sheath in front of the transverse process of the cervical spine, and deep cervical lymph nodes exist nearby. After respiratory tract infection, the lymph nodes are enlarged, possibly stimulating the nerves and further developing symptoms of occipital neuralgia. We believe that the etiology of occipital neuralgia is complex and could be the earliest manifestation of severe diseases. When occipital neuralgia is accompanied by fever, the possibility of infectious diseases should be considered.

CONCLUSION

The etiology of occipital neuralgia is complex and could be the earliest manifestation of severe diseases. When occipital neuralgia is accompanied by fever, the possibility of infectious diseases should be considered. Avian influenza is one of these causative agents.

FOOTNOTES

Author contributions: Zhang J conducted data curation and project management, reviewed and analyzed data, supervised the entire study, wrote the manuscript, read and approved the final manuscript.

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CASE REPORT

Gefitinib improves severe bronchorrhea and prolongs the survival of a patient with lung invasive mucinous adenocarcinoma: A case report

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Abstract

BACKGROUND

Lung invasive mucinous adenocarcinoma (LIMA), formerly referred to as mucinous bronchioloalveolar carcinoma, is a rare disease that usually presents as bilateral lung infiltration, is unsuitable for surgery and radiotherapy, and shows poor response to conventional chemotherapy.

CASE SUMMARY

We report a 56-year-old Chinese man with a history of smoking and epidermal growth factor receptor mutation-positivity who was initially misdiagnosed as severe pneumonia, but was ultimately diagnosed as a case of invasive mucinous adenocarcinoma of the lung by computed tomography -guided percutaneous lung biopsy. Bronchorrhea and dyspnea were improved within 24 h after initiation of gefitinib therapy and the radiographic signs of bilateral lung consolidation showed visible improvement within 30 d. After more than 11 months of treatment, there is no evidence of recurrence or severe adverse events.

CONCLUSION

Although the precise mechanism of the antitumor effects of gefitinib are not clear, our experience indicates an important role of the drug in LIMA and provides a reference for the diagnosis and treatment of this disease.

Key Words: Gefitinib; Epidermal growth factor receptor; Lung cancer; Bronchorrhea; Lung invasive mucinous adenocarcinoma; Case report

Core Tip: Gefitinib improves severe bronchorrhea and prolongs the survival of a patient with lung invasive mucinous adenocarcinoma.

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INTRODUCTION

Lung cancer is the second most common cancer worldwide and the leading cause of cancer-related deaths, accounting for almost one-quarter of all cancer-related deaths[1]. Non-small cell lung cancer (NSCLC) is the main pathological type of lung cancer, accounting for about 80%–85% of all cases of lung cancer[2,3]. In the 2015 World Health Organization classification of lung tumors, lung invasive mucinous adenocarcinoma (LIMA) is classified as a variant of invasive lung adenocarcinoma, which accounts for approximately 5%–10% of lung adenocarcinomas[4]. The diagnostic hallmark of invasive mucinous adenocarcinoma (IMA) is tall columnar cell morphology with abundant intracellular/extracellular mucus and invasive adenocarcinoma patterns (such as acinar, lepidic, papillary, and predominant patterns)[5]. The clinical presentation of LIMA is different from that of other subtypes of adenocarcinoma. LIMA typically shows diffuse lung involvement, which results in severe respiratory symptoms, such as bronchorrhea and dyspnea[6,7]. In addition, LIMA also tends to be resistant to conventional chemotherapy, and patients typically have a short survival time after detection of the cancer[8].

Recent years have witnessed important breakthroughs in the treatment of NSCLC, which has evolved from traditional surgery, chemotherapy, and radiotherapy to the era of molecular targeted therapy and immunotherapy. The development of epidermal growth factor receptor (EGFR) targeted tyrosine kinase inhibitors (TKIs) have helped facilitate the concept of personalized cancer therapy into a reality[9]. Several studies have demonstrated high antitumor activity of EGFR-TKIs against bronchioloalveolar carcinoma and the therapeutic response can be dramatic and long-lasting[10,11]. Gefitinib is a reversible EGFR targeted TKI that competes for Mg-ATP binding sites in the EGFR catalytic region, thereby blocking signaling, inhibiting cancer cell proliferation, and inhibiting mitogen-activated protein kinase activation, inducing cancer cell apoptosis[12].

Here, we report a patient with LIMA who was successfully treated with gefitinib. Bronchorrhea and dyspnea were improved within 24 h after treatment with gefitinib, and the radiographic signs of bilateral lung consolidation were visibly improved within 30 d. As of 11 mo after initiation of gefitinib, there are no signs of tumor progression.

CASE PRESENTATION

Chief complaints

On October 29, 2021, a 53-year-old man presented to the department of respiratory medicine at our hospital due to shortness of breath and excessive sputum production for 3 mo.

History of present illness

As shown in Figure 1, the patient expectorated large amount of white and foamy sputum (approximately 700 mL/d), accompanied by chest tightness and shortness of breath. He was earlier treated with oral amoxicillin and expectorants, but the results were not satisfactory.

History of past illness

The patient had no prior chronic disease, but had recently lost 2 kg of his body weight.

Personal and family history

He was a chronic smoker (20 cigarettes per day for more than 10 years). The patient denied having a family history of lung cancer, hypertension, or coronary heart disease.

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Figure 1 Image shows 700 mL/d watery sputum produced by the patient.

Physical examination

Vital signs at admission were as follows: Body temperature, 37.8°C; heart rate, 114/min; respiratory rate, 30/min; blood pressure, 147/110 mmHg; oxygen saturation, 90% (under nasal cannula 5 L/min oxygen inhalation). Physical examination revealed coarse crackles in both lungs.

Laboratory examinations

Blood gas analysis showed respiratory failure with an oxygen partial pressure (PaO_2) of 54 mmHg and oxygenation index of 129 mmHg. Conventional inflammation markers [C-reactive protein: 1.37 mg/mL (reference range, 0–10), procalcitonin: 0.05 ng/mL (< 0.05), white blood cell count: 10.9 × 10^9/L (4–10 × 10^9), absolute neutrophil count: 6.35 × 10^9/L (1.8–6.3 × 10^9), and neutrophil percentage: 58.3% (40%–75%)] were measured on the day of clinical examination. No obvious abnormalities were found in coagulation, sputum smear microscopy, sputum culture, tuberculosis bacilli gamma interferon release test, rheumatoid factor, liver and kidney function, tumor markers (carcinoembryonic antigen, cytokeratin, neuron-specific enolase), connective tissue related antibodies, or anti-neutrophil cytoplasmic antibody.

Imaging examinations

Chest high-resolution computed tomography scan showed large flaky hyperintense shadows in both lungs, especially in the right lung (Figure 2).

FINAL DIAGNOSIS

The clinical picture was suggestive of infectious pneumonia and he was administered routine anti-infection, expectorant, and antispasmodic treatment. However, the patient showed no symptomatic improvement after 3 d of treatment. Bronchoscopy was performed to further clarify the cause, which showed a lot of white secretions in the trachea (Figure 3). The right lower lobe was lavaged and sent for next-generation sequencing (NGS). However, NGS results showed no pathogens. Repeat chest computed tomography (CT) performed on the 7th day of treatment showed an increase in the lung solid lesions compared with those on admission, while there was no significant change in inflammatory marker levels. Subsequently, the patient underwent CT-guided percutaneous lung biopsy, which confirmed the diagnosis of LIMA (Figure 4). In addition, the tissue specimen was subjected to *EGFR* analysis. Systematic investigations revealed no metastases other than the lungs, and based on clinical and histological findings, the patient was diagnosed with stage IV disease. Fortunately, genetic testing revealed positive *EGFR-21* mutation (c.2573T>G:p.L858R).

TREATMENT

Other medications were discontinued, and treatment with an EGFR-tyrosine kinase inhibitor, gefitinib (250 mg/d) was commenced.

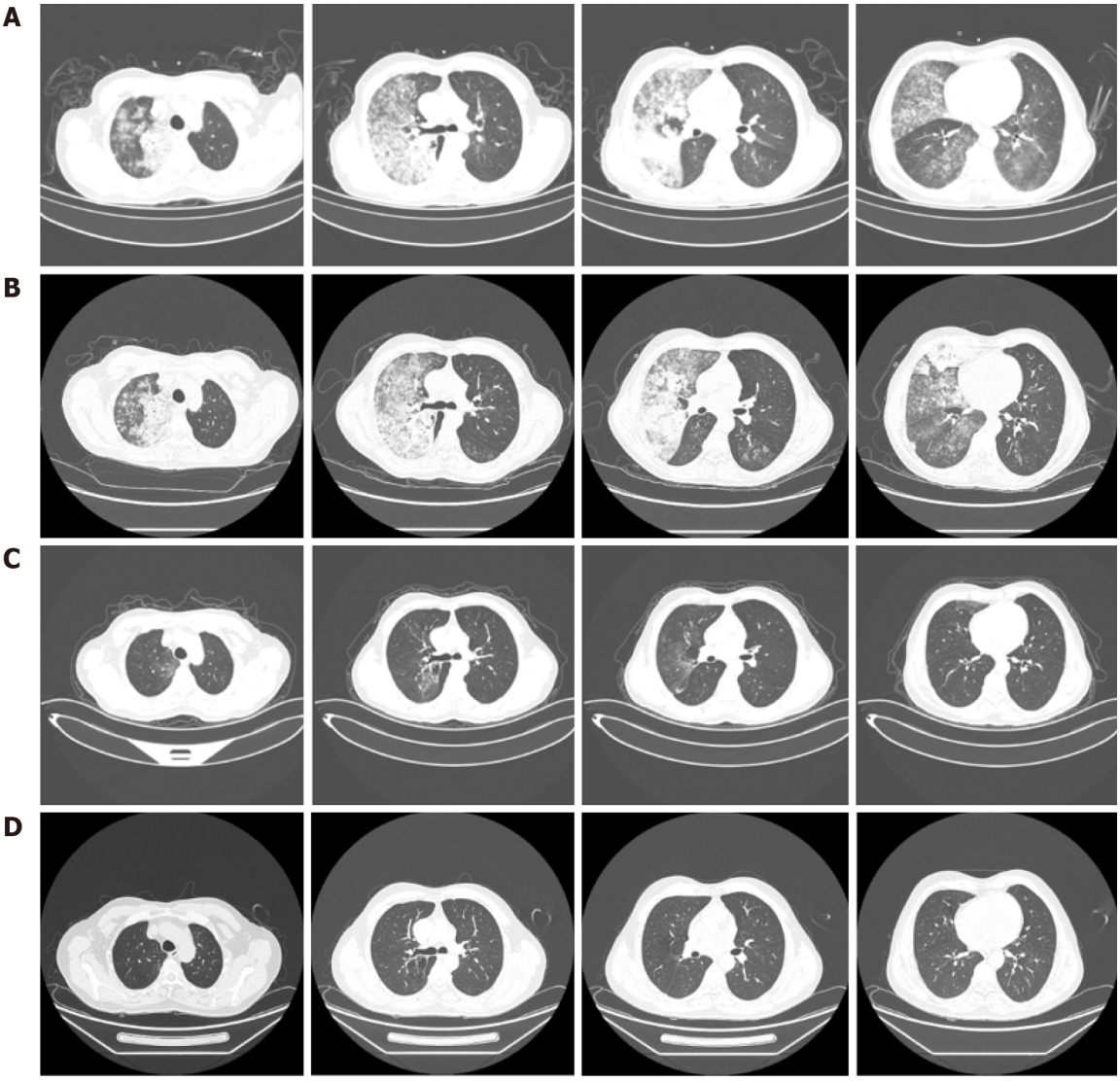

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Figure 2 Chest computed tomography findings. A: At the beginning of treatment; B: Anti-infection treatment lasted for 1 wk; C: Gefitinib was treated for 1 mo; D: Gefitinib was treated for 11 mo. Chest high-resolution computed tomography scan shows large flaky hyperintense shadows in both lungs, especially in the right lung. A-D show the chest computed tomography images at the first diagnosis, after anti-infection treatment for 1 wk, after treatment with gefitinib for 1 mo, and after treatment with gefitinib for 11 mo, respectively.

OUTCOME AND FOLLOW-UP

Twenty-four hours after initiation of treatment, the patient showed remarkable improvement in symptoms with alleviation of dyspnea and bronchorrhea. Arterial blood gas analysis showed a PaO_2 of 81 mmHg and oxygenation index of 279 mmHg upon nasal inhalation of 2 L/min O_2. The volume of sputum discharged decreased from 700 to 300 mL/d, and 3 d later it was further reduced to 100 mL/d. Chest CT scan showed remarkable improvement of infiltration 30 d (Figure 2) after treatment. After more than 11 mo of treatment (Figure 2), there was no evidence of recurrence or severe adverse events.

DISCUSSION

Adenocarcinoma is the most commonly diagnosed pathological subtype of NSCLC. LIMA was recognized as a distinct subtype of lung adenocarcinoma with unique biological properties, as well as a different prognosis compared with other lung adenocarcinoma subtypes[13]. Previous studies have shown that LIMA may originate from type II alveolar epithelial or Clara cell metaplastic lesions, and further develop atypical hyperplasia and carcinogenesis[14,15]. Tumor cells in IMAs are highly discrete, and show poor adhesion; These easily diffuse widely through alveolar pores and small airways, which is an important reason for their diffuse distribution[16,17]. In a study by Cha *et al*[18], 13.9% of IMAs were initially identified as pneumonia, which is much higher than the rate of initial misdiagnosis of

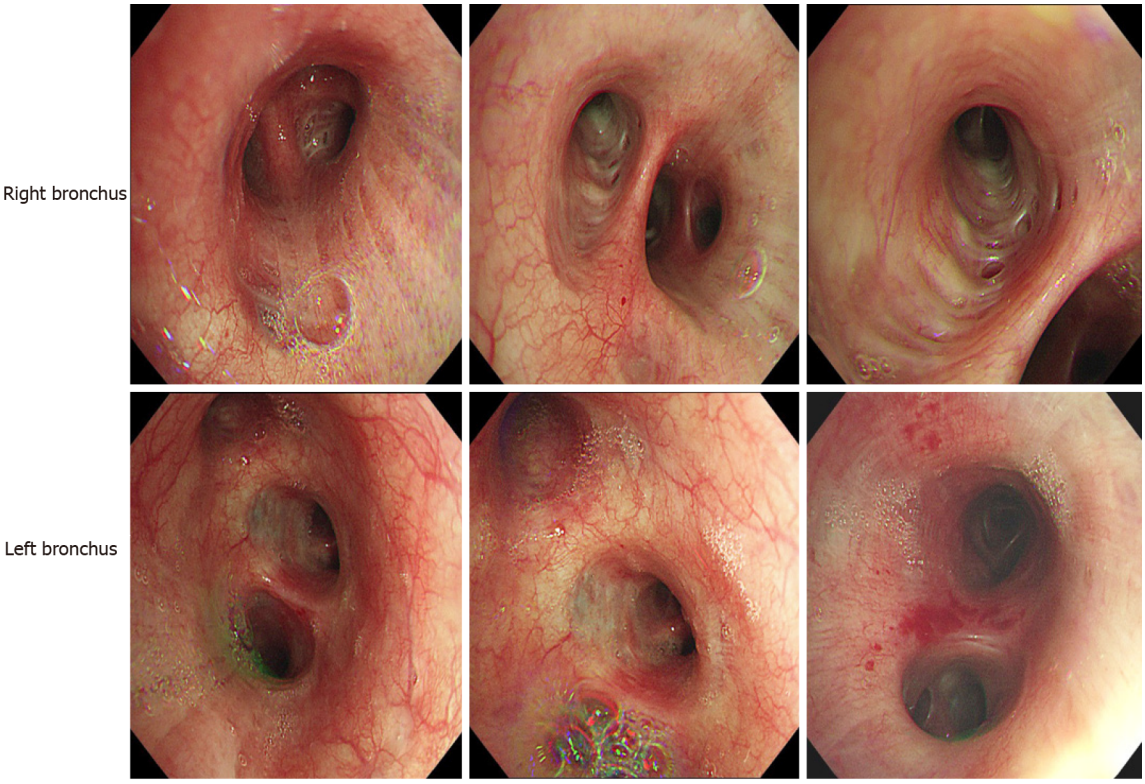

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Figure 3 Bronchoscopy findings of the case. There are a lot of white secretions in the trachea.

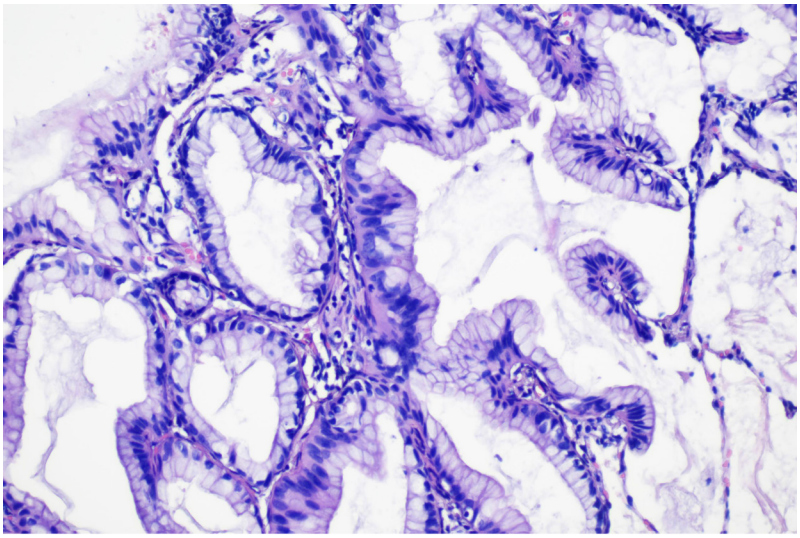

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Figure 4 Histopathological section of computed tomography -guided percutaneous lung biopsy specimen showing lung invasive mucinous adenocarcinoma (H&E stain, 200×).

invasive non-mucinous adenocarcinomas as pneumonia. Nie *et al*[19] analyzed the data of 40 patients with mucinous adenocarcinoma who underwent surgical resection; they found that 25% patients showed either pneumonia-like consolidation or multifocal patchy consolidation on chest CT. Invasive mucinous adenocarcinoma and pneumonia are not easy to distinguish due to the large overlap of clinical features, including cough and sputum symptoms[20].

This was also an important reason why this case was initially misdiagnosed as pneumonia. For middle-aged and elderly patients, those with pulmonary infiltrates that are not absorbed by anti-infection treatment, and who continue to experience cough with expectoration of large amount of white sputum, the possibility of pneumonia-type lung cancer should be considered and a pathological

diagnosis obtained. Pathology is still the gold-standard for the diagnosis of the disease, and the accurate diagnosis of LIMA is a key imperative to initiate appropriate treatment and improve the prognosis.

Advances in the field of molecular profiling and targeted therapies have brought about a paradigm shift in the treatment landscape for NSCLC[21]. Lung adenocarcinoma patients with genetic mutations can achieve prolonged survival with corresponding targeted therapy. According to previous studies reporting gene mutation analysis in the context of LIMA, KRAs are the most common mutation type accounting for approximately 35%–75%, while the incidence of Tp53 mutation is approximately 46%; the incidence of *EGFR* mutation, *ALK* rearrangement, and *BRAF* mutation is very low[22-24]. However, several studies have demonstrated high antitumor activity of EGFR-TKIs against LIMA, and the therapeutic response can be dramatic and long-lasting. In 2013, López-González *et al*[25] described a 66-year-old woman diagnosed with right lung IMA who tested positive for *EGFR* mutation; treatment with gefitinib led to significant shrinkage of lesions, and the patient showed a long progression-free survival. Moreover, Pastorino *et al*[26] claimed that long-term gefitinib therapy may be effective in the management of atypical adenomatous hyperplasia and multifocal IMA presenting as diffuse ground glass opacities, when fluorescence in situ hybridization or molecular testing are indicative of sensitivity.

Our patient was *EGFR* mutation-positive for which the recommended treatment is gefitinib. This treatment resulted in a rapid reduction of bronchorrhea, associated with a dramatic improvement in dyspnea, hypoxia, and radiographic abnormalities. Gefitinib is an orally-active, selective EGFR-TKI that blocks signal transduction pathways implicated in the proliferation and survival of cancer cells[27]. Of note, some studies have reported contradictory findings about LIMA without *EGFR* mutation treated with gefitinib[28,29].

CONCLUSION

At present, the exact mechanism of action of targeted drugs for tumors is not fully understood. Owing to the low number of patients treated with these drugs, further research and follow-up studies are required to obtain more definitive evidence.

FOOTNOTES

Author contributions: All authors have read and approved the manuscript, and significantly contributed to this paper. Ou GC, Luo W, Zhang WS, Wang SH, Zhao J, Zhao HM, and Qiu R contributed to conception and design, literature review, manuscript writing and correction, final approval of manuscript; Ou GC and Luo W contributed equally to this work; All authors read and approved the final manuscript.

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CASE REPORT

Habitual khat chewing and oral melanoacanthoma: A case report

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Abstract

BACKGROUND

Habitual khat (*Catha edulis*) chewing has been proven to cause numerous oral tissue changes. However, oral melanoacanthoma triggered by chronic khat chewing is rare. Oral melanoacanthoma is an uncommon, sudden, asymptomatic, benign pigmentation of the oral cavity. Under the microscope, the epithelial layer of the oral mucosa showed dendritic melanocyte proliferation and acanthosis. The study aimed to highlight chronic khat chewing as a trigger for oral melanoacanthoma.

CASE SUMMARY

In the current study, we report a case of a 26-year-old male patient with a rare presentation of oral melanoacanthoma triggered by regular khat chewing. Many intrinsic and extrinsic factors can cause oral pigmentation. Chewing khat is an extrinsic factor that can cause several diseases, including oral pigmentation. In this case, the definitive diagnosis was oral melanoacanthoma. This diagnosis was made based on the patient's history, clinical lesion presentation, and microscopic biopsy results.

CONCLUSION

Habitual khat (*Catha edulis*) chewing causes many oral tissue changes including oral melanoacanthoma. The study aimed to highlight chronic khat chewing as a trigger for oral melanoacanthoma.

Key Words: Oral melanoacanthoma; Oral lesion; Qaat chewing; Oral pigmentation; Brown

pigmentation; Benign lesion; Case report

Core Tip: Habitual khat chewing causes many oral tissue changes including oral melanoacanthoma. Oral melanoacanthoma is a rare and benign oral pigmentation rarely triggered by khat chewing. The patient in the current case with a khat chewing habit presented with unilateral, diffused, and dark pigmentation in the oral mucosa.

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INTRODUCTION

Habitual khat (*Catha edulis*) is commonly found in a few parts of Africa and many countries in the Middle East, such as the Arabian Peninsula. In some cultures, it has been associated with social customs. Recently, with global migration, khat chewing habits have reached the United States, Europe, and Australia[1,2]. Khat chewing is customarily practiced at prolonged social gatherings called khat sessions, lasting several hours each day. The custom usually entails inserting and chewing fresh khat leaves to form a bolus that is held in the lower buccal vestibule against the check on one side or, in rare cases, on both sides. At the end of the session, the quid is expelled, while the juice is partially expectorated and absorbed[3,4].

Fresh khat leaves have psychoactive, sympathomimetic, and euphoric effects caused by a principal alkaloid known as cathinone, which is structurally similar to amphetamine. Khat users chew fresh or dried leaves and buds[5,6]. Many studies have shown that chewing fresh khat leaves causes mood swings, depression, insomnia, hypertension, ischemic heart disease, anorexia, and constipation. Khat is not associated with addiction, but may lead to psychosomatic dependence[7].

Chewing khat causes several potentially harmful systemic health effects, including renal toxicity, gastrointestinal and liver problems, and cardiovascular abnormalities. In addition, long-term khat consumption has been linked to several oral and dental conditions, including keratotic white lesions, mucosal pigmentation, plasma cell stomatitis, teeth attrition and loss, discoloration, temporomandibular joint issues, gingival recession, and periodontal infections[8]. In animals, khat increases the free radicals that cause tissue damage. Thus, high doses of the active ingredient of khat are released into the oral fluids and most of it is absorbed into the oral tissues[9].

Oral melanoacanthoma is an uncommon, sudden, asymptomatic, benign pigmentation of the oral cavity. It typically occurs suddenly and is clinically characterized by diffused, rapidly growing, dark brown to black colored, and macular tissue pigmentation. It commonly affects the buccal mucosa (51.4%), the palate and lips (15%-22%), and the gingiva (> 6%)[10]. African Americas and younger patients are more likely to develop oral melanoacanthoma[11]. Histopathological analysis has revealed dendritic melanocyte dispersion and acanthosis of the superficial epithelium[12]. Oral melanoacanthoma is self-limiting in nature and is secondary to tissue trauma, which stimulates melanocytic activity. It disappears after eliminating irritants or biopsy. This strengthens the reactive nature of the lesions[13].

The Clinical differential diagnosis of oral pigmentation includes several topical and systemic causes. This study aimed to highlight chronic khat chewing as a trigger for oral melanoacanthoma. A review of the literature revealed a few cases of oral melanoacanthoma caused by chewing khat (*Catha edulis*). This case report describes a rare, unilateral case of oral melanoacanthoma caused by khat chewing in a 26-year-old male patient: "The work has been reported in line with the SCARE criteria"[14].

CASE PRESENTATION

Chief complaints

A 26-year-old healthy male Saudi individual with a khat chewing habit of approximately 100 g of khat/2 sessions daily for more than 12 years visited the oral medicine clinic at Dental Hospital, King Saud University, for the examination of oral brown pigmentations.

History of present illness

The patient had a 4-mo history of asymptomatic, unilateral diffuse brown oral pigmentation that appeared abruptly and diffused rapidly. He had discontinued chewing khat upon noticing the oral discoloration. Oral pigmentation was not associated with weight loss, fatigue, or night sweats in this study. The patient reported that he had undergone routine dental follow-up. The patient had no history of drinking soft drinks, chewing tobacco or shisha, smoking, consuming betel nuts, or heavy metal exposure.

History of past illness

The patient was unaware of any medical condition and was not consuming any medications.

Personal and family history

He was unaware of any hereditary conditions.

Physical examination

Physical and systemic examination: Physical examination revealed no remarkable skin rash, ascites, jaundice, or any other abnormal findings. The patient had a slightly elevated blood pressure of 122/79 mmHg, a height of 167 cm, and a weight of 75 kg.

Extraoral examination: Extraoral examination revealed no significant findings.

Intraoral examination: On intraoral examination, the patient had full dentition and no clinical dental caries; however, he had poor oral hygiene, tooth discoloration, and a yellowish tongue. The right buccal mucosa, right upper and lower vestibules, soft palate, right upper and lower gingiva, and floor of the mouth were all found to have unilateral, asymptomatic, smooth, macular brownish-black pigmentation with ill-defined margins (Figure 1A and B). The oral cavity showed no signs of leukoplakia, stomatitis, xerostomia, periodontal disease, or keratotic white lesions.

Laboratory examinations

The blood results were within normal limit; a white blood cell count of 9.7 × 10^3/ mL; a red blood cell count of 5.1 × 10^6/mL; a platelet count of 319 × 10^3/ mL; a hemoglobin count of 14.2 g/dL; cortisol 21 mcg/dL; adrenocorticotropic hormone, 9.1 pmol/L; a blood urea nitrogen value of 24 mg/dL; serum creatinine value of 0.97 mg/dL; potassium, 4.6 mmol/L; sodium, 137 mmol/L; albumin, 49 g/L; total bilirubin of 18 μmol/L; alanine aminotransferase, 48 IU/L; aspartate aminotransferase, 52 IU/L; and alkaline phosphatase, 294 IU/L.

DIFFERENTIAL DIAGNOSIS

The differential diagnoses of this case included oral melanoacanthoma, physiologic pigmentation, medication-induced pigmentation, Addison's disease, and melanoma.

FURTHER DIAGNOSTIC WORK-UP

After discussing the possible diagnosis with the patient, an incisional biopsy was performed to confirm the diagnosis. The potential risks of surgical and postsurgical consequences, such as infection, delayed wound healing, bleeding, swelling, pain, discomfort, and scarring, were discussed in detail. Written informed consent was obtained from the patient. After administering 1.8 mL of anesthetic solution (lidocaine HCl 2% and epinephrine 1:100000) intraorally *via* an injection to the buccal mucosa, three soft tissue specimens (5 mm each) were obtained from the darkest areas of the lesion. Theincisions were sutured using Vicryl sutures. Verbal and written instructions were also provided.

Three gross specimens were fixed in 10% neutral buffered formalin and then sent as three pieces in separate cassettes for histopathological analysis. Histopathological examination of hematoxylin and eosin (H&E)-stained sections revealed acanthosis, spongiosis, and parakeratinized stratified squamous epithelium with mild chronic inflammation in the lamina propria of the connective tissue. Multiple dendritic melanocytes were observed in the epithelium (Figure 2A). Additionally, Melan-A-stained tissue sections revealed melanocytic hyperplasia throughout the epithelium with no features of malignancy (Figure 2B and C).

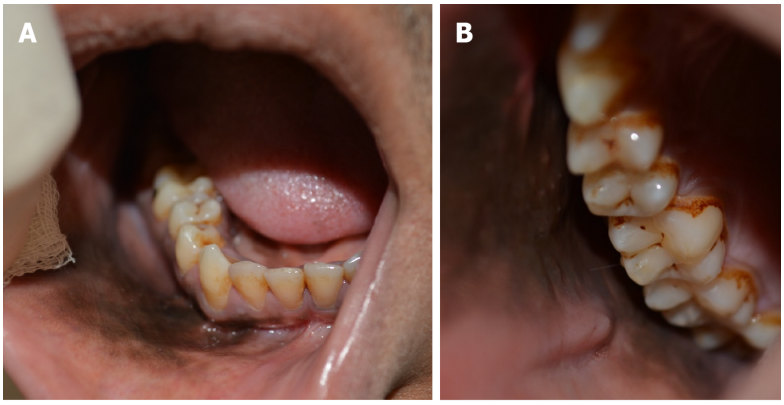

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Figure 1 Intraoral examination. A and B: Clinical photos of the oral cavity illustrate a diffuse dark brownish-black pigmented lesion with an ill-defined margin covering the right lower gingiva, right buccal and labial vestibules, and right buccal mucosa.

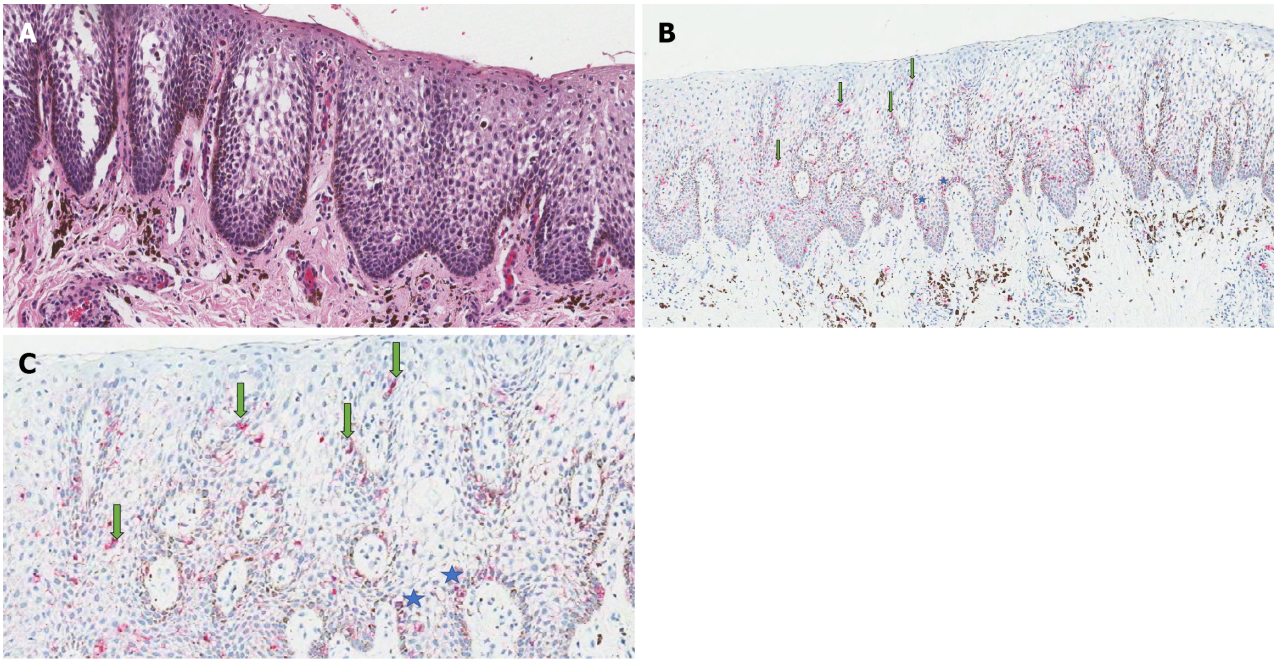

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Figure 2 Histopathological photomicrographs. A: Histopathological photomicrograph of Hematoxylin and Eosin stained section shows spongiosis, acanthosis, and dendritic melanocytes in the parakeratinized stratified squamous epithelium. Also, show the lamina propria with melanin deposit; B: Histopathological photomicrograph of Melan-A-stained section shows dendritic melanocytes (green arrows) and melanocytic hyperplasia (blue stars) throughout the epithelium; C: Histopathological photomicrograph (higher magnitude) of Melan-A-stained section shows dendritic melanocytes (green arrows) and melanocytic hyperplasia (blue stars) throughout the epithelium.

FINAL DIAGNOSIS

Based on the patient's history, clinical lesion presentation, and microscopic biopsy result, the definitive diagnosis was oral melanoacanthoma.

TREATMENT

The patient was reassured regarding the benign nature of the lesion and was advised to quit chewing khat. Although thelesions appear unpleasant, the pigmentation is harmless and self-limiting and generally disappears without medical intervention.

OUTCOME AND FOLLOW-UP

During the 2-mo follow-up visit, the pigmentation disappeared partially (Figure 3A). During the 4-mo follow-up visit, the lesions disappeared completely (Figure 3B). Consequently, the patient discontinued chewing khat owing to the possibility of developing malignant lesions.

DISCUSSION

Khat chewing may cause mechanical and chemical irritation to the oral tissues. As a result, khat induces oral tissue changes, such as tooth discoloration, dental caries, white and red lesions, mucosal hyperpigmentation, periodontal diseases, and mouth dryness. In animals, khat hampers the body's ability to clear free radicals. Consequently, free radicals can cause tissue damage. Chronic khat chewers generally keep the khat bolus in the oral vestibule for hours. Therefore, high doses of the active ingredient of khat, "alkaloid cathinone," are released into the oral fluids and most of it is absorbed into the oral tissues[9]. Melanin production increases in areas of irritation that cause pigmented lesions. Melanin protects against environmental stressors such as ultraviolet radiation and reactive oxygen species. The purpose of increased melanocyte proliferation and production of melanin in the epithelium is to protect and produce a balanced microenvironment that contributes to tissue homeostasis[15].

In this case report, the patient had been a chronic khat chewer for more than 12 years. Hence, for a long time, the khat bolus was in direct contact with the oral soft tissues. After eliminating all other possible causative factors, it was believed that the mechanical and chemical irritation to the oral tissues caused by khat triggered the oral melanoacanthoma in the current case. Oral melanoacanthoma is a rare, asymptomatic, reactive-pigmented lesion that was first documented in 1927 by Bloch[16]. It is described as an ill-defined, flat, or slightly elevated macule, which is diffused, solitary, or multifocal, and dark brown to black in color. It is generally asymptomatic and measures > 1 cm in diameter within a few weeks[17]. Moreover, oral melanoacanthomas possess no potential for malignant transformation. Melanoacanthoma etiopathogenesis is not precisely understood; however, in general, the clinical presentation of pigmentation is suggestive of a reactive lesion caused by mechanical irritation[18].

Clinically, the differential diagnosis includes chewing khat, medication-induced pigmentation, physiological pigmentation, amalgam tattoos, graphite implantation, hygiene products, Addison's disease, Peutz-Jeghers syndrome, McCune-Albright syndrome, post-inflammatory lichen planus, oral melanotic macules, acquired melanotic nevus, metal poisoning, and melanoma. Most of these entities can be ruled out with a precise history, as oral melanoacanthoma can grow suddenly and rapidly in size in a matter of weeks. Moreover, oral melanoacanthoma has an excellent prognosis. Notably, pigmented lesions, in most reported cases, faded gradually following minor trauma or after cessation of the causative agents[19].

Histologically, H&E-stained tissues illustrate hyperplastic and parakeratinized stratified squamous epithelium with long rete ridges and acanthosis. Melanin deposits can be observed in the lamina propria. In addition, many benign dendritic melanocytes have dendritic processes throughout the epithelium[20]. Additional melanocytic markers, such as Melan-A or MART-1, tyrosinase, and HMB-45, can be used to confirm the diagnosis of pigmented lesions[21].

The present clinical case has several advantages. A thorough medical and dental history was recorded, a complete clinical examination was performed, and multiple incisional soft tissue biopsies were obtained from the three darkest spots of the pigmented macule. Histopathological examination confirmed oral melanoacanthoma. The patient agreed to quit chewing khat, and the lesion disappeared gradually 4 mo after the oral biopsy.

CONCLUSION

In general, knowing the etiology of the problem through effective medical history-taking would save time and assist in proper diagnosis. This study aimed to highlight chronic khat chewing as a trigger for oral melanoacanthoma. Further studies are needed to understand the exact effects of chronic khat chewing on oral melanoacanthoma.

PATIENT PERSPECTIVE

The resolution of the pigmented lesion had a positive impact on the patient's life, as he discontinued chewing khat owing to the possibility of developing malignant lesions. Moreover, the patient regained confidence after the pigmented lesion disappeared.

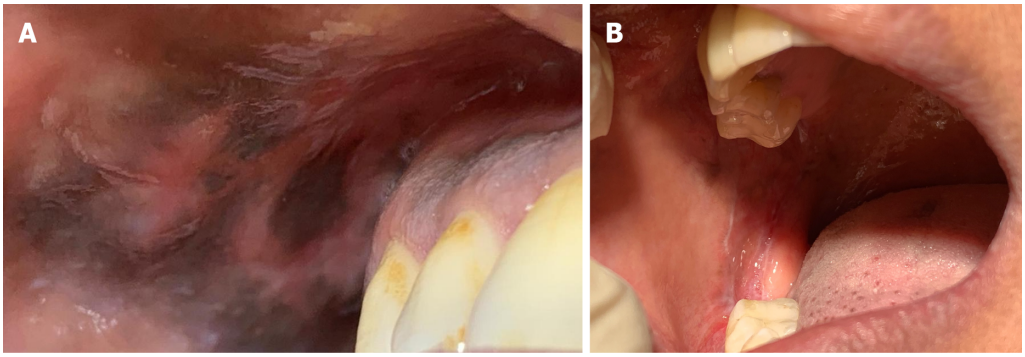

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Figure 3 Follow-up clinical photos. A: Two-month follow-up clinical photos of the right buccal mucosa showing partial resolution of the oral lesion; B: A 4-mo follow-up clinical photo of the oral cavity illustrates the complete resolution of the oral melanoacanthoma.

FOOTNOTES

Author contributions: Albagieh HN served as the patient's oral medicine specialist and contributed to data collection; Aloyouny AY reviewed the literature and contributed to data collection, data interpretation, and manuscript drafting; Alshagroud RS served as the patient's oral pathology specialist and contributed to data collection and data interpretation; Alwakeel AA, Alkait SS, Almutairi GG, Almufarji FS, and Alkhalaf RS contributed to data collection, data interpretation, manuscript drafting, and manuscript revision; all authors have issued final approval for the version to be submitted.

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CASE REPORT

Systemic lupus erythematosus with multicentric reticulohistiocytosis: A case report

Ping-Ping Liu, Zong-Wen Shuai, Li Lian, Kang Wang

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Abstract

BACKGROUND

Multicentric reticulohistiocytosis (MRH)/systemic lupus erythematosus (SLE) overlap syndrome is an uncommon disease in the clinic and is diagnosed through characteristic clinical manifestations, histopathology, and immunopathology. Here, we report the case of a 30-year-old woman with SLE who developed MRH.

CASE SUMMARY

A 30-year-old woman with a history of polyarthritis for the past 12 years had multiple skin nodules on her body for 10 years, including the sacrococcygeal area, dorsum of the hands, interphalangeal joint of the feet and sternoclavicular joint. The histopathology of a biopsy of the distal interphalangeal joint of the hands revealed granulomatous inflammation, fibrous hyperplasia with ground-glass degeneration, inflammatory cell exudation and focal necrosis. The immunohistochemical stains showed positive staining for CD68 and negative staining for S100 and acid-fast staining. The patient was diagnosed with SLE with MRH. Her symptoms were improved after a combined treatment of prednisone, hydroxychloroquine and cyclophosphamide.

CONCLUSION

MRH/SLE overlap syndrome is difficult to diagnose and treat. Cyclophosphamide may be an alternative choice for the treatment of MRH.

Key Words: Multicentric reticulohistiocytosis; Systemic lupus erythematosus; Cyclophosphamide; Systemic disorder; Case report

Core Tip: We present a case of systemic lupus erythematosus with multicentric reticulohistiocytosis that was reported for the second time. Multicentric reticulohistiocytosis/systemic lupus erythematosus overlap syndrome is an uncommon disease that is hard to diagnose and treat. This case illustrates how to diagnose and treat the comorbidities and the connection that exists between them. For treatment, cyclophosphamide may be an alternative choice for multicentric reticulohistiocytosis.

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INTRODUCTION

Multicentric reticulohistiocytosis (MRH) is a rare, multisystem non-Langerhans cell disorder of unknown etiology that is characterized by erosive polyarthritis and skin papulonodular lesions. MRH is associated with underlying malignancy and autoimmune disease, including breast cancer, ovarian adenocarcinoma, melanoma, rheumatoid arthritis (RA), Sjogren's syndrome, systemic lupus erythematosus (SLE) and multiple sclerosis[1,2]. Many cases are misdiagnosed as RA due to the manifestation of arthritis mutilans, including symmetric articular involvement, marginal erosion in bone and severe arthritis destruction. Herein, we report a case of SLE with MRH.

SLE is an autoimmune disease involving multiple organs and is associated with substantial morbidity. Active SLE may develop into a rare, difficult-to-diagnose macrophage activation syndrome (MAS) in both adults and pediatric patients[3,4]. MAS is a very severe, acute and potentially life-threatening condition that is considered a secondary form of hemophagocytic lymphohistiocytosis. It is also a serious complication of many rheumatic diseases and is associated with potential malignancy[5]. In addition to destruction of joints and skin, persistent high-grade fever, hepatosplenomegaly, lymphadenopathy and central nervous dysfunction are the main clinical manifestations, which should be used to differentiate from MRH[3,4]. There are no established treatment guidelines for the management of MRH because of its rarity and infrequency[6]. Our case of SLE with MRH is surprisingly responsive to cyclophosphamide (CTX).

CASE PRESENTATION

Chief complaints

A 30-year-old woman with a history of polyarthritis for the past 12 years was accompanied by multiple skin nodules on her body for 10 years.

History of present illness

A 30-year-old woman with a history of polyarthritis for the past 12 years was accompanied by multiple skin nodules on her body for 10 years. Relevant tests observed leukopenia, hemolytic anemia, high titer of antinuclear antibody (ANA), positive anti-Sm antibody, RNP, SSA, SSB and lupus band test, and a low level of complement C3. The patient was diagnosed with SLE according to the 2019 European League Against Rheumatism and the American College of Rheumatology criteria[7]. The symptoms of polyarthritis improved after treatment with 60 mg prednisone and 10 mg leflunomide once a day. However, two years after the diagnosis, a peanut-sized nodule was noticed on the sacrococcygeal area of the patient. The nodule gradually increased in size and was accompanied by an ulceration and a purulence. The biopsy showed fibrous hyperplasia with infiltration of multinuclear giant cells and necrosis, which was in line with the secondary changes of epidermal cysts. Several new papulonodular lesions appeared involving the dorsum of the hands, interphalangeal joint of the feet, and sternoclavicular joint, occasionally with an ulceration. Hyperplasia of fibrous tissue with multinucleated giant cell infiltration and foam cell formation was observed in biopsy. However, the diagnosis of the nodule remains unknown.

The patient was admitted to the hospital with new skin nodules on the distal interphalangeal of the hands and feet and a mass over the right sternoclavicular joint (Figure 1). The lesion is firm and has no tenderness. Laboratory tests showed hypersensitivity C-reactive protein (hs-CRP), and the erythrocyte sedimentation rate (ESR) was increased. The anti-cyclic citrullinated peptide (CCP) antibody titer was 10 RU/mL; furthermore, the tuberculosis infection T-lymphocyte spot test (T-SPOT) result was positive. ANA was strongly positive with a titer of 1:1000. A positive result was found for anti-centromere B antibody, anti-La/SS-B antibody, anti-SSA (52) and anti-SSA (60) antibody. X-ray of the hands showed

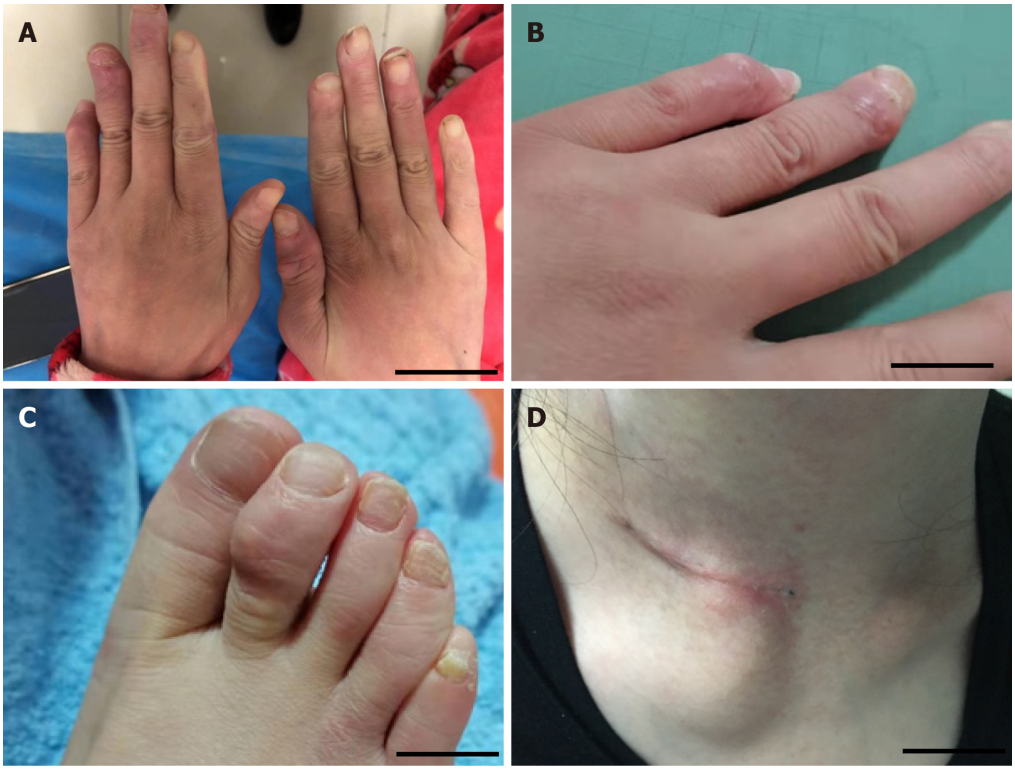

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Figure 1 The patient was admitted to the hospital with new skin nodules on the distal interphalangeal of the hands and feet and a mass over the right sternoclavicular joint. A and B: Papulonodular lesions over the interphalangeal joint of the both hands; C: Feet; D: Right sternoclavicular joint. Scale bar = 50 μm.

bone erosion at the distal interphalangeal joints with the appearance of a pencil-in-cup deformity (Figure 2). Magnetic resonance imaging (MRI) of the hip joint revealed ischemic necrosis and synovitis in the left femoral head.

The biopsy of the nodules on the distal interphalangeal joint of the right hand revealed fibrous hyperplasia with ground-glass degeneration, inflammatory cell exudation and focal necrosis. Urate deposition was observed within the fibrous area. The immunohistochemical stains showed positive staining for CD68 but negative staining for both S-100 and acid-fast stain (Figure 3). These findings, along with clinical manifestations, were suggestive of MRH. Therefore, the patient was diagnosed with SLE with MRH on the basis of her history and relevant auxiliary examination.

History of past illness

She had a history of SLE for 12 years.

Personal and family history

There was no clinically significant family history, the patient had no smoking or drinking habits, and she did not have a history of using illicit drugs or exposure to toxic substances.

Physical examination

A local round bulge could be seen near the clavicle in the IV region of the right neck, approximately 3 cm × 2 cm in size, soft in texture, and no tenderness. Multiple round masses around the upper part of the right humerus, bilateral fingers and toes were observed.

Laboratory examinations

The anti-CCP antibody titer was 10 RU/mL; and the T-SPOT result was positive. ANA was strongly positive with a titer of 1:1000. A positive result was found for anti-centromere B antibody, anti-La/SS-B antibody, anti-SSA (52) and anti-SSA (60) antibody.

The white blood cells, red bloods cells, platelets, hemoglobin, erythrocyte sedimentation rate and hypersensitivity C-reactive protein levels are summarized in Table 1.

Imaging examinations

An X-ray of the hands showed bone erosion at the distal interphalangeal joints with the appearance of a pencil-in-cup deformity (Figure 2). MRI of the hip joint revealed ischemic necrosis and synovitis in the

Table 1 White blood cells, red bloods cells, platelets, hemoglobin, erythrocyte sedimentation rate, hypersensitivity C-reactive protein levels

Timeline	WBC (× 10^9/L)	RBC (× 10^{12}/L)	PLT (× 10^9/L)	HGB (g/L)	ESR (mm/h)	hs-CRP (mg/L)
August 2020	3.52	3.80	169	111	23↑	17↑
September 2020	4.79	2.89↓	270	82↓	28	79.38↑
October 2020	4.78	4.12	209	109↓	19	1.92
February 2021	2.53↓	3.79↓	110↓	111↓	21↑	10.79↑
May 2021	7.10	4.21	219	124	12	4.49
May 2022	4.56	3.83	209	125	10	3.50

WBC: White blood cells; RBC: Red bloods cells; PLT: Platelets; HGB: Hemoglobin; ESR: Erythrocyte sedimentation rate; hs-CRP: Hypersensitivity C-reactive protein.

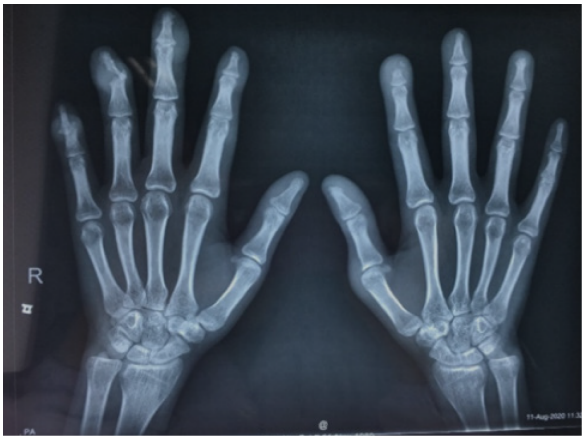

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Figure 2 X-ray of both hands showed bone erosion at the distal interphalangeal joints with appearance of a pencil-in-cup deformity and articular soft tissue swelling.

left femoral head.

The biopsy of the nodules on the distal interphalangeal joint of the right hand revealed fibrous hyperplasia with ground-glass degeneration, inflammatory cell exudation and focal necrosis. Urate deposition was observed within the fibrous area. The immunohistochemical stains showed positive staining for CD68 but negative staining for both S-100 and acid-fast stain (Figure 3).

FINAL DIAGNOSIS

The patient was diagnosed with SLE with MRH.

TREATMENT

There is no specific treatment for this disease. Her treatment regimen consisted of 7.5 mg prednisone, 200 mg hydroxychloroquine and 10 mg leflunomide, all once a day orally to control the primary disease. After consultation with the Department of Bone Disease Orthopedics Oncology, a biopsy of the lump at the 4/5th distal interphalangeal joint of the right hand was performed under anesthesia, and the postoperative pathology was in line with MRH. Once a week, 10 mg methotrexate (MTX) was administered for treatment. However, poor response to MTX after 6 mo of treatment was recorded for the patient, and new nodules were detected on her hands and feet. Since the regimen was replaced with prednisone and 0.4 g CTX intravenous infusion once every two weeks accordingly, the patient has not complained about the new nodules anymore.

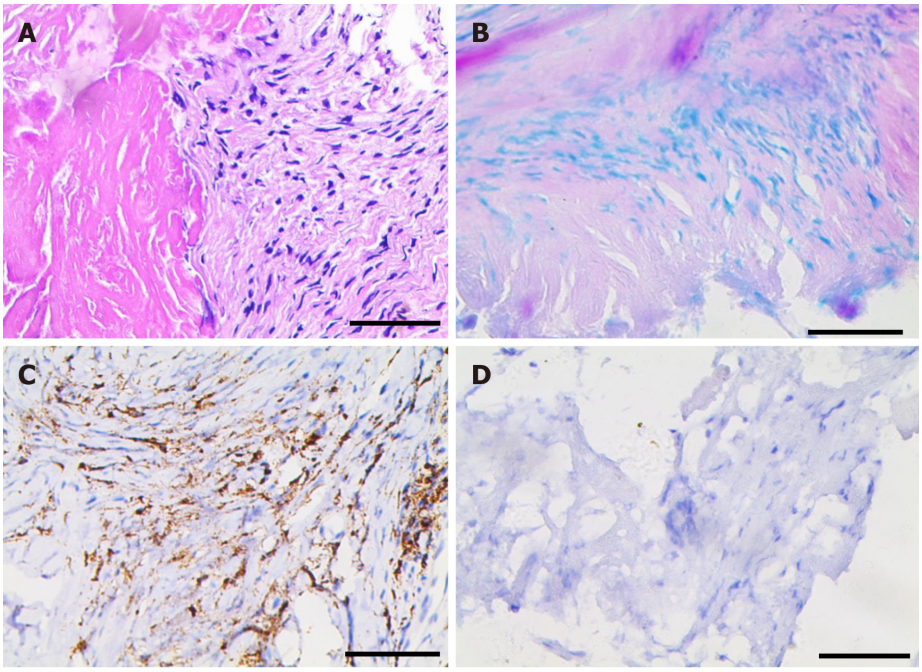

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Figure 3 Immunohistochemical staining (with 40 × magnification). A: Hematoxylin-eosin stain; B: Acid-fact stain; C: Positive for CD68; D: Negative for S100). Scale bar = 50 μm.

OUTCOME AND FOLLOW-UP

The current follow-up is one year, with no new systemic manifestations and few outbreaks of limited cutaneous nodular lesions.

DISCUSSION

MRH is a rare multisystem disease of unknown etiology. It can be divided into two types: reticular histiocytoma localized to the skin and erosive polyarthritis and nodular skin lesions[8]. The onset of the disease is insidious, mostly in middle-aged women approximately 40 years old[2]. Many patients are misdiagnosed with RA, and the following clues can help to understand the disease. Initially, polyarthritis is usually symmetric, and distal interphalangeal joints are affected in 75% of patients[9]. The skin is nonpruritic, and reddish-brown papules and nodules are seen on the forearms, forehead, neck and upper trunk, varying from a few millimeters to 2 cm in size[8]. Histopathological examination often reports multinucleated giant cell infiltration and foam cell formation, which need to be differential diagnoses with tuberculosis infection and lupus panniculitis. The histopathological examination of the patient reported foam cell formation. Considering the previous diagnosis of SLE, it is easy to misdiagnose it as lupus panniculitis that occurred predominantly on the fat-rich area, which was hardly suggestive of erosive arthritis. Immunohistochemical staining is positive for CD45 and CD68 but negative for S100 and CD1a, which is characteristic of Langerhans cells in MRH[9,10]. In addition, eosinophilic cytoplasm with a ground-glass appearance was also observed. All of these factors lead to the possibility of other proliferative and destructive diseases.

MRH has been reported to be associated with a variety of autoimmune diseases, which are often accompanied by RA, Sjogren's syndrome, primary biliary cirrhosis, systemic vasculitis and SLE[2,9]. Other concomitant conditions include tuberculosis infection, tumor and gout, which were also recorded in our patient. A positive T spot result was reported in our case, consistent with a literature report that some patients have a positive skin PPD test[11]. Our patient was also diagnosed with a left fallopian tube cyst and underwent surgery one month later, consistent with the report that up to 25% of patients have reported malignancies, such as breast, cervical, ovarian, and stomach tumors[9,12]. Last, the pathological biopsy of our patient reported urate deposition, which may be because urate is prone to be deposited under acidic conditions, consistent with the report that the MRH patient has thyroid disease and gout[13,14].

MRH may be associated with various autoimmune diseases in approximately 29% of cases[6]. In our case report, laboratory findings, including high ANA titers (1:1000), elevated ESR, leukopenia and hypocomplementemia, were all suggestive of active SLE, and this patient consistently had small lumps

on different parts of the body. When SLE was in a stable state, the progression of MRH also appeared to be in remission. This is consistent with the relationship between MRH and SLE activity reported by Saito *et al*[15]. The mechanism of association between MRH and SLE remains unknown, which may reflect a coincidence or a common pathogenesis[6]. However, it is interesting to show trends in the expression of class II human leukocyte antigen DR (HLA DR) and proinflammatory cytokine elevation, including tumor necrosis factor-α (TNF-α), interleukin (IL)-6 and IL-12, which are secreted by macrophages and lymphocytes in both disorders. In SLE, the class II HLA DR genes play a role in conferring disease susceptibility, clinical and immunological expression, and levels of TNF-α, IL-6 and IL-12 are high in the serum of lupus patients compared to heathy controls[16,17]. Meanwhile, in MRH, the macrophage-specific marker of class II HLA DR is expressed in synovial fluid of mononuclear cells from patients with arthritis. Furthermore, quantitative amounts of the proinflammatory cytokines TNF-α, IL-6 and IL-12 are elevated in synovial fluid and serum[6]. Bennàssar *et al*[10] detected a decrease in proinflammatory cytokines after treatment in MRH. According to the above data, it is noteworthy that progression and resolution of MRH may correlate with SLE disease activity by the upregulation of soluble factors, such as cytokines, and hyperactivity of macrophages and lymphocytes, suggesting that immunological disorders might participate in the pathogenesis of MRH.

Given the rare and infrequent presentation of this disease, there are no established treatment guidelines for the management of MRH. Considering the high risk of progressive joint destruction and potentially disfiguring skin lesions, effective and timely therapy is crucial to patient outcomes. Limited evidence supports the use of nonsteroidal anti-inflammatory drugs and disease-modifying antirheumatic drugs commonly used in rheumatoid arthritis, including MTX, leflunomide, hydroxychloroquine, azathioprine, CTX and cyclosporin A, and in some cases combined with biologic treatment [6]. As MRH is associated with elevated TNF levels, anti-TNF agents are able to block TNF, and adalimumab and infliximab were proven to be valid for MRH treatment. Sarilumab and tocilizumab have been proposed as specific immunomodulators to treat MRH refractory patients based on the overexpression of IL-6 in the giant multinucleated cells of the MRH inflammatory infiltrate, which play a vital role in improving joints and dermatological manifestations. Meanwhile, a recent case report mentions that using anakinra (IL-1 inhibition) allowed for control of the disease[1]. In our patient, we initially treated with prednisone, hydroxychloroquine, leflunomide and MTX, but the patient failed to respond to MTX, with new nodules detected on her hands and feet after 6 mo of treatment. Since the regimen was replaced with prednisone and CTX, the patient has had a striking improvement in symptoms. It has been reported that CTX was of significant benefit in 20% of cases, with complete arthritis resolution, and in 27% of cases of skin lesions in MRH. Additionally, partial arthritis and skin disease control was seen in 40 and 45% of cases, respectively[1]. However, the precise mechanism of CTX was not documented, but it can be postulated. CTX may regulate MRH-related immunological abnormalities since it is known to inhibit the production of the proinflammatory cytokines IL-6 and IL-12, which are secreted by macrophages and lymphocytes[18,19]. This disrupts these cytokine-based communication networks between macrophages and lymphocytes. The cytokines IL-6 and IL-12 always rely on the JAK-STAT pathway to lead to the formation of granulomas and erosion of arthritis. CTX does not rule out reversing the progression of MRH through the JAK-STAT pathway[19].

CONCLUSION

MRH and SLE are both multisystem diseases. The involvement of erosive arthritis and skin papulonodular lesions are important clues in distinguishing MRH from SLE. Cyclosporine has been reported to be effective in MRH with SLE, while CTX was also effective in this case. We refer to the possible mechanism of CTX in MRH and propose CTX as an alternative choice for the treatment of MRH.

FOOTNOTES

Author contributions: Liu PP and Wang K designed the study; Liu PP, Lian L, Shuai ZW and Wang K collected data and performed analyses; Liu PP drafted the manuscript; Wang K edited and revised manuscript; all authors contributed to the article and approved the submitted version.

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CASE REPORT

X-linked Charcot-Marie-Tooth disease after SARS-CoV-2 vaccination mimicked stroke-like episodes: A case report

Qiang Zhang, Yang Wang, Run-Tao Bai, Bao-Rong Lian, Yu Zhang, Li-Ming Cao

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Abstract

BACKGROUND

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccinations have been administered worldwide, with occasional reports of associated neurological complications. Specifically, the impact of vaccinations on individuals with X-linked Charcot-Marie-Tooth disease type 1 (CMTX1) is unclear. Patients with CMTX1 can have stroke-like episodes with posterior reversible encephalopathy syndrome on magnetic resonance imaging (MRI), although this is rare.

CASE SUMMARY

A 39-year-old man was admitted with episodic aphasia and dysphagia for 2 d. He received SARS-CoV-2 vaccination 39 d before admission. Physical examination showed *pes cavus* and reduced tendon reflexes. Brain MRI showed bilateral, symmetrical, restricted diffusion with T2 hyperintensities in the cerebral hemispheres. Nerve conduction studies revealed peripheral nerve damage. He was diagnosed with Charcot-Marie-Tooth disease, and a hemizygous mutation in the *GJB1* gene on the X chromosome, known to be pathogenic for CMTX1, was identified. Initially, we suspected transient ischemic attack or demyelinating leukoencephalopathy. We initiated treatment with antithrombotic therapy and immunotherapy. At 1.5 mo after discharge, brain MRI showed complete resolution of lesions, with no recurrence.

CONCLUSION
SARS-CoV-2 vaccination could be a predisposing factor for CMTX1 and trigger a sudden presentation.

Key Words: X-linked Charcot-Marie-Tooth disease; SARS-CoV-2 vaccination; Stroke-like episodes; Reversible splenial lesion syndrome; Demyelinating leukoencephalopathy; Case report

Core Tip: We present a case report of a young man who presented with episodic aphasia and dysphagia after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination. After a complete neurological evaluation, nerve conduction study, and DNA analysis, we diagnosed the patient with Charcot-Marie-Tooth disease type 1 (CMTX1). CMTX1 can occur after SARS-CoV-2 vaccination, and thus SARS-CoV-2 vaccination should be considered a potential predisposing factor for CMTX1. There is paucity of information on the neurological consequences of SARS-CoV-2 vaccination, even though billions of vaccines have been administered worldwide. We believe that our study makes a significant contribution to the literature based on the continued urgency of the coronavirus disease 2019 pandemic.

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INTRODUCTION

Charcot-Marie-Tooth disease (CMT) is an inherited neuropathy that mainly affects the motor and sensory fibers of the peripheral nervous system. The prevalence of CMT is 1/2500[1,2]. X-linked CMT type 1 (CMTX1) results from mutations in the *GJB1* gene on chromosome Xq13.1[3,4] and is the second most common form of CMT[5,6]. A small number of patients with CMTX1 present with episodic neurological dysfunction and reversible white matter lesions, which have not been adequately reported.

Billions of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccinations have been administered worldwide, and there have been occasional reports of central nervous system (CNS) complications caused by the vaccination[7]. In a study of 704300 subjects receiving the first dose of an mRNA SARS-CoV-2 vaccination, 65% had at least one neurologic manifestation, including headache (62.2%), transient paresthesia (3.5%), and weakness (1%). There were also reports of serious adverse events, including seizures, Guillain-Barré syndrome, and transverse myelitis[7]. Some patients experienced severe neurological complications after vaccination, including cerebral venous sinus thrombosis, CNS demyelinating diseases, inflammatory peripheral neuropathies, and limbic encephalitis[8]. The impact of vaccination on individuals with CMTX1 is unclear at present.

In this report, we present the case of a patient with CMTX1 and stroke-like episodes after SARS-CoV-2 vaccination with reversible splenial lesion syndrome (RESLES). We have reviewed the relevant literature to raise attention to the impact of SARS-CoV-2 vaccination on CMTX1 expression.

CASE PRESENTATION

Chief complaints

A 39-year-old man presented with three episodes of acute-onset aphasia and dysphagia over 2 d in June 2021.

History of present illness

The patient was vaccinated with an inactivated SARS-CoV-2 vaccine (Beijing Institute of Biological Products Co., Ltd., Beijing, China)[9]. He received the first dose of the vaccine 2 mo before admission and the second dose 39 d before admission. Two days before admission, the patient reported aphasia and dysphagia for 1 h. Later that night, he had a second episode with similar symptoms as well as dyspnea, which lasted for approximately 1 h. Asyndesis, dysphagia, and dyspnea developed over 3 h on the morning of admission, which prompted his visit to our emergency department.

History of past illness

He had eczema and renal calculus for many years, and his eczema recurred after the second vaccine. He denied any history of major trauma or toxin exposure.

Personal and family history

He has three brothers, one with *pes cavus* and another with *pes cavus* and CMT. His parents denied any history of hereditary diseases. His mother had died of myocardial infarction.

Physical examination

Physical examination showed that the patient was alert and had demonstrated weakness in chewing and swallowing, difficulty in tongue thrusting, difficulty in lifting the soft palate, diminished tendon reflexes of the limbs, mild atrophy of the muscles of the hands and distal leg, and bilateral *pes cavus*. There were no other positive neurological signs.

Laboratory examinations

Blood analysis after admission showed that erythrocyte sedimentation rate, serum creatinine, electrolyte, glycosylated hemoglobin, and D-dimer levels were within normal limits. Laboratory tests showed slightly increased white blood cell count (11.75 × 10^9/L; reference range: 3.5–9.5 × 10^9/L), hepatitis B surface antigen levels (73.05 IU/mL; reference range: 0–0.03 IU/mL), antistreptolysin-O titers (218.00 IU/mL; reference range: 0–200 IU/mL), and total cholesterol levels (5.64 mmol/L; reference range: < 5.2 mmol/L).

Imaging examinations

Initial head computed tomography (CT) showed no obvious abnormalities (Figure 1A). Brain magnetic resonance imaging (MRI) (Figure 1B-F) on day 2 showed bilateral, symmetrical, and restricted diffusion (Figure 2A-D), with T2 hyperintensities in the corpus callosum and supratentorial white matter. The neostigmine test, repetitive nerve stimulation, chest CT, carotid artery Doppler ultrasound, echocardiography, transcranial Doppler, CT angiography (Figure 1G), and electroencephalography showed no obvious abnormalities. Contrast-enhanced transcranial Doppler revealed a small, natural, or consecutive right-to-left shunt. Transesophageal echocardiography also showed a small intracardiac right-to-left shunt. A 24-h dynamic electrocardiogram showed accidental atrial premature beats, paroxysmal ventricular tachycardia, and paroxysmal ST-segment change.

MULTIDISCIPLINARY EXPERT CONSULTATION

On day 25 after discharge, genetic sequencing (Beijing Golden Standard Medical Laboratory, Beijing, China) results showed a hemizygous mutation (c.65 G>A p.R22Q) in the *GJB1* gene (Figure 3).

FINAL DIAGNOSIS

CMTX1.

TREATMENT

Initially, we suspected that he was experiencing transient ischemic attack or demyelinating leukoencephalopathy at admission. We began immunotherapy [intravenous (IV) immunoglobulin 27.5 g/day and IV methylprednisolone 500 mg/day, followed by IV dexamethasone 10 mg/day for 5 d]; antiplatelets (aspirin and clopidogrel), improving cerebral metabolism (IV deproteinized calf serum extract[10,11]) and improving cerebral circulation (IV Erigeron breviscapus[12]); hypolipidemic agent (atorvastatin); and symptomatic therapy. His symptoms improved on the afternoon of admission. Brain MRI on day 4 showed that the lesions were not enhanced (Figure 1H), and the areas of restricted diffusion were obvious but not reduced (Figure 2E-H). Nerve conduction studies revealed prolonged compound muscle action potential, reduced amplitude, and slowed motor velocity in both the median (right 35.3 m/s; left 39.2 m/s) and tibial (right 31.1 m/s; left 33.4 m/s) nerves, and slowed sensory conduction velocity in both sural nerves. The results suggested both myelin dysfunction and axonal damage, especially in the distal limbs. Based on the clinical and laboratory examinations, we diagnosed him with CMT. He was discharged on day 7 and felt no discomfort with reduced tendon reflexes at discharge. He was satisfied with the treatment received, as well as his recovery.

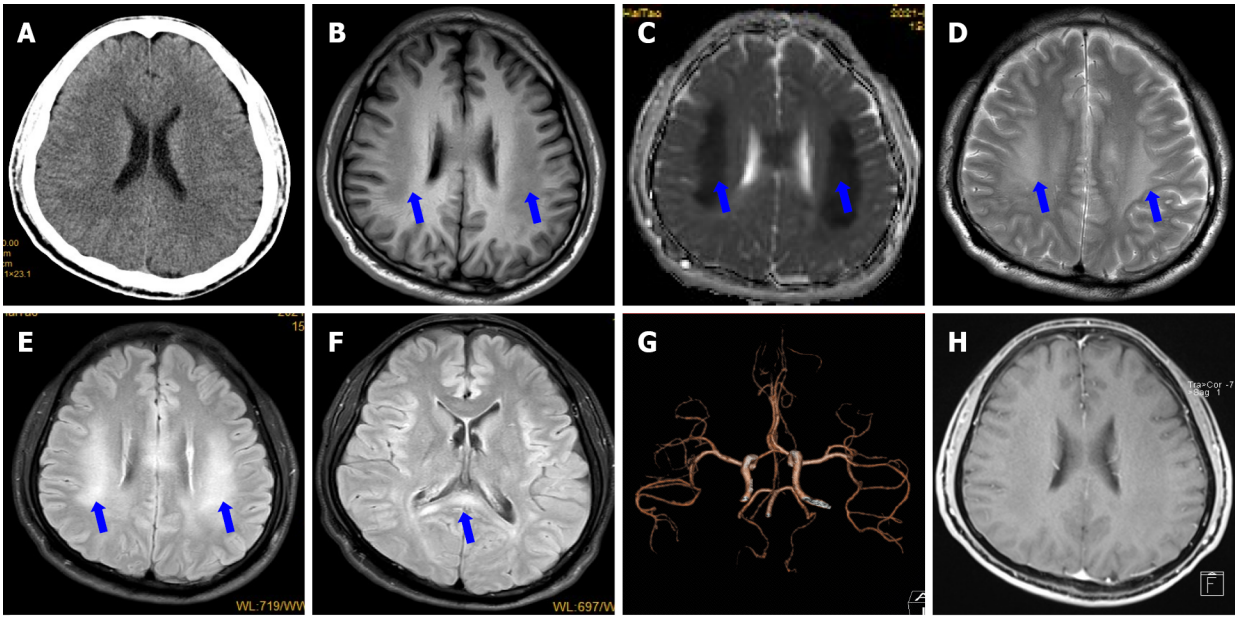

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Figure 1 Initial magnetic resonance imaging findings. A: Initial head computed tomography (CT) shows no obvious abnormalities; B: Magnetic resonance imaging (MRI) on day 2 showed bilateral, symmetric, and definite hypointensities with T1-weighted imaging (blue arrows); C and D: Hypointensities on apparent diffusion coefficient mapping (C) and T2-weighted imaging (D) (blue arrows); E and F: Hyperintensities on fluid-attenuation inversion recovery sequence in the corpus callosum and supratentorial white matter (blue arrows); G: CT angiography shows no obvious abnormalities; H: Contrast-enhanced MRI on day 4 shows that the lesions were not enhanced.

OUTCOME AND FOLLOW-UP

At 1.5 mo after discharge, a follow-up appointment showed that he had no discomfort, and a repeat MRI showed complete resolution of the lesions (Figure 2I-L).

DISCUSSION

In this report, we presented the case of an older patient with CMTX1 with the primary symptom of repeated posterior circulation stroke-like episodes accompanied by RESLES, after a SARS-CoV-2 vaccination. We speculate that SARS-CoV-2 vaccination may be a predisposing factor for CMTX1, resulting from a hemizygous mutation in the *GJB1* gene on chromosome Xq13.1. However, there are few research reports on this topic.

The most common predisposing factors for CMTX1 are infection or fever, high-altitude travel, and intense exercise[13]. However, this patient did not have any of these predisposing factors before the onset. We must consider the possibility that the SARS-CoV-2 vaccine may be associated with developing CMTX1, even though this potential relationship is not clear. However, we are highlighting a clinical research question to bring this possibility to broader attention.

Our patient had a relatively late onset of the disease after vaccination. Most patients have symptom onset within a short period after vaccination. Most neurological symptoms in patients (71.8%) with CNS demyelination occurred approximately 9 d after vaccination[14]. All patients who developed Guillain-Barré syndrome after the first dose of the vaccine (Dose 1) had a latency of 3−22 d[15]. Twenty-one cases with severe neurological complications were diagnosed within a median of 11 (range 3–23) d after SARS-CoV-2 vaccinations[8]. However, there are also some reports of later-onset cases after vaccination. A female patient with post-vaccination acute disseminated encephalomyelitis presented with a first seizure 1 mo after the second SARS-CoV-2 vaccine (Dose 2)[16]. There have been three cases of Bell's palsy after SARS-CoV-2 vaccination that occurred on day 37 after Dose 1, day 32 after Dose 2, and day 48 after Dose 2, respectively[17]. Although most neurological symptoms appeared after Dose 1, some patients had onset after Dose 2. In another study, approximately 73% of patients (n = 8) developed a rash after SARS-CoV-2 vaccine Dose 1, and 27% of patients (n = 3) after the second dose[18]. Our patient had neurological side effects after Dose 2.

The mechanism of neurological events possibly caused by SARS-CoV-2 vaccination is not well-understood, but we speculate that it may be related to inflammation. The activation or reactivation of the immune system is thought to be the most likely cause[19]. Some experts believe cellular mechanisms may involve breaking gap junctions between oligodendrocytes and astrocytes, causing the inability of

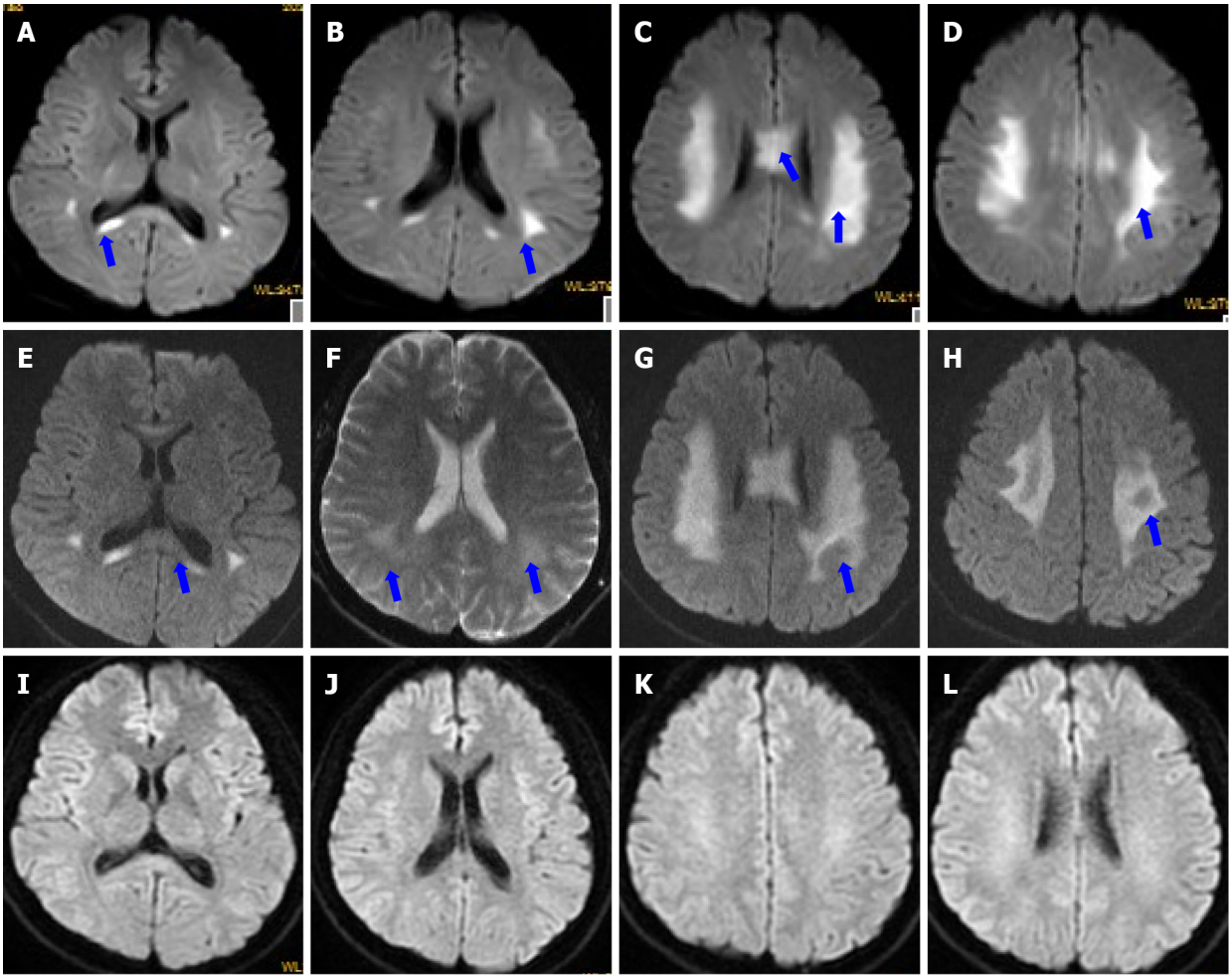

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Figure 2 Dynamic changes in diffusion-weighted imaging. A-D: Diffusion-weighted imaging (DWI) on day 2 showed that the corpus callosum (A-C) and bilateral centrum semiovale (B-D) had marked abnormally restricted diffusion (blue arrows); E-H: DWI on day 4 showed that the areas of restricted diffusion were obvious (F and G) but not reduced (blue arrows); I-L: DWI at 1.5 mo after discharge shows that the lesions disappeared.

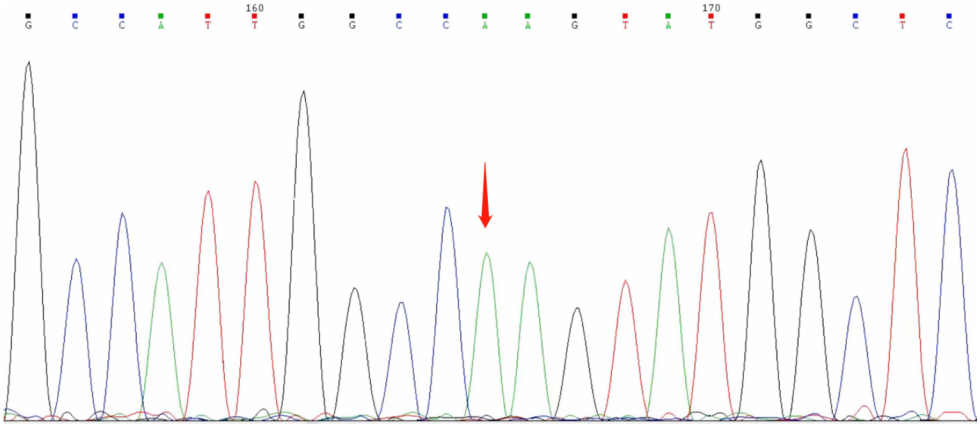

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Figure 3 Genetic sequencing (Beijing Golden Standard Medical Laboratory, Beijing, China) results showed a hemizygous mutation (c.65 G>A p.R22Q) in the *GJB1* gene.

these cells to regulate fluid exchange[20]. All types of vaccines inevitably evoke immune responses. Consequently, some immune diseases recur or worsen after vaccination. In our patient, eczema recurred after the second dose of the vaccine. Additional reports of immune-related exacerbations include a report of a man with renal-limited microscopic polyangiitis, which recurred 5 wk following the first

dose[21]. Fourteen patients with psoriasis experienced an exacerbation soon after the second vaccine [22]. There are reports of patients with varicella-zoster virus reactivation induced by Dose 2[23], as well as aggravation of cutaneous lupus erythematosus following the mRNA vaccine[24]. An intense immune response may cause aggravation of a pre-existing autoimmune disease and may even trigger *de novo* autoimmune diseases[24]. Immune disorders are closely related to neuropathies or neurological complications, especially immune-mediated neuropathies[25].

CMTX1 is highly heterogeneous, presenting initially with CNS symptoms, and can be misdiagnosed. The most common CNS manifestations of patients with CMTX1 include periodic dysarthria, ataxia, hemiparesis[26], dysphagia, facial or lingual weakness, and numbness, in addition to cranial nerve deficits, aphasia, chorea, dizziness, and lethargy. CNS symptoms manifest as facial-lingual paresis or limb weakness in 93.6% of patients, difficulty speaking or swallowing in 83.0%, hypoesthesia in 31.9%, and ataxia in 21.3%[13]. The presence of foot deformity or a characteristic consistent with X-linked inheritance increases the possibility of CMT.

The patient in this report, who was initially suspected of having demyelinating encephalopathy, began his treatment with immunotherapy. Interestingly, a report of 27 patients with CMTX1 showed that 14 (51.9%) received corticosteroid and/or IV immunoglobulin therapy after presenting CNS symptoms[13]. This suggests that we should not only distinguish CMTX1 from stroke but also from acute disseminated encephalomyelitis and adrenoleukodystrophy in clinical practice. It is important to perform a detailed family history evaluation and neurological examination. This patient had a strong family history, which is important for validating this diagnosis. A positive family history, weakened tendon reflexes, and *pes cavus* support a diagnosis of CMTX1.

While our patient was older, CMTX1 with transient CNS manifestations is typically a disorder that mainly affects children and adolescents[26]. This patient had reversible, bilateral, non-enhancing leukoencephalopathy and restricted diffusion on MRI, which presented with RESLES; these are characteristics of the CNS imaging phenotype of CMTX1[26]. Abnormal signals were most often found in deep brain white matter (88.9%) and the corpus callosum (80.0%) on MRI of patients with CMTX1 with episodic CNS deficits[13]. Mutations in connexin 32, produced from *GJB1*, are responsible for most CMTX1 cases[2].

We found that brain MRI abnormalities are one of the key features of patients with CNS involvement. After an attack, the MRI usually shows increased T2-weighted, fluid-attenuated inversion recovery (FLAIR), diffusion-weighted hyperintense signals in bilateral deep white matter, and the corpus callosum with sparing of the subcortical U fibers. We observed that the abnormal MRI signals reversed after an attack. CMTX1 should be considered another rare cause of RESLES. We observed the abatement of the clinical symptoms followed by the resolution of the T2/FLAIR abnormal signals. A repeated brain MRI showed that the lesions did not disappear but became even more obvious. Nerve conduction studies in this patient were consistent with the characteristics of CMT-related peripheral nerve damage, including prolonged latency, reduced amplitude, and slowed conduction velocity. Forearm nerve conduction velocities (NCV) are typically in the "intermediate" range of 30–40 m/s for males. An important signal is the median nerve, which has a motor NCV of 25−45 m/s and can be easily detected [13]. In male patients with CMT, it is often no more than 38 m/s in the median nerv[27].

There is currently no specific treatment for CMT, and treatment is mainly symptom-based, in addition to the avoidance and elimination of predisposing factors. The patient's symptoms were rapidly relieved after immunotherapy, and there has been no recurrence to date. Therefore, immunotherapy may be an effective treatment for vaccine-related CMTX1 onset. The CNS phenotype of CMTX1 has a good prognosis for the patient's CNS function[28], and recognition will avoid unnecessary tests and potentially harmful therapy.

CMT disease is a rare entity and thus its flare up from vaccination can happen in extremely few cases. It is not yet possible to draw conclusions about any significant association between SARS-CoV-2 vaccination and CMTX1. Similar cases and population cohorts should be scrutinized to ensure the constant evaluation of such risks.

CONCLUSION

CMTX1 can occur without warning after SARS-CoV-2 vaccination, and the vaccination should be considered a potential predisposing factor. This relationship requires further attention and research. CMTX1 can mimic stroke-like episodes, and RESLES is a feature of the MRI phenotype of CMTX1.

FOOTNOTES

Author contributions: Cao LM was involved in writing, diagnosis confirmation, and conceptualization; Zhang Q and Wang Y were involved in writing, constructive discussion, and literature review; Zhang Y, Lian BR, and Bai RT provided constructive discussion; All authors have read and approved the final manuscript; Zhang Q and Wang Y contributed equally to this work and share first authorship.

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CASE REPORT

Acute liver injury in a COVID-19 infected woman with mild symptoms: A case report

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Abstract

BACKGROUND

Coronavirus disease 2019 (COVID-19) has spread rapidly, resulting in a pandemic in January 2020. Few studies have focused on the natural history and consequences of acute liver injury (ALI) in mild or asymptomatic COVID-19 patients, manifested by elevated aminotransferase levels. ALI is usually expected for severe COVID-19 cases. Here, we present a COVID-19 case with mild respiratory symptoms and significantly elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels.

CASE SUMMARY

A 60-year-old woman without medical history or chronic illness received three COVID-19 vaccinations since the start of the pandemic. The patient was infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and presented with mild symptoms on July 12th, 2022. Post-recovery, she underwent an examination at our hospital on August 30th, 2022. AST and ALT levels in the liver function test were 207 U/L (normal value < 39, 5.3-fold increase) and 570 U/L (normal value < 52, 10.9-fold increase), respectively. The patient was diagnosed with ALI, and no treatment was prescribed. The following week, blood tests showed a reduction in both levels (ALT 124 U/L, AST 318 U/L). Two weeks later, AST and ALT levels had decreased to near the expected upper limits (ALT 40 U/L, AST 76 U/L).

CONCLUSION

Clinicians should pay attention to liver function testing during COVID-19 recovery regardless of the disease's severity.

Key Words: COVID-19; Hepatitis; Pneumonia; Aspartate aminotransferase; Alanine aminotransferase; Case report

Core Tip: Even though elevated aminotransferase levels and acute liver injury (ALI) are expected for severe coronavirus disease 2019 cases, here we report a rare case of ALI following a mild infection. We provide detailed information on ALI's natural course in such patients.

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INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread rapidly, resulting in a pandemic in January 2020[1]. The major clinical symptoms of COVID-19 include respiratory disease and respiratory failure[2]. In addition to the characteristic respiratory symptoms, COVID-19 has extrapulmonary manifestations, including acute kidney injury, myocarditis, cardiac dysfunction, the risk of developing type 1 diabetes, thrombosis, and acute liver injury (ALI)[3-5].

A significant proportion of COVID-19 patients presenting with elevated liver enzymes have been reported worldwide[6]. The prevalence of ALI has ranged from 16% to 53% in COVID-19 patients[7]. Elevated aminotransferase levels are often mild [1-2 times the upper limit of normal (UNL)], while severe cases with much higher aminotransferase levels (UNL > 5) have also been observed[2,8]. Severe liver injury occurred in only 6.4% of the affected patients, and it is associated with poor clinical outcomes, including respiratory failure requiring intubation, renal replacement therapy, intensive care unit admission, and death[6,9]. Alterations in liver enzyme levels are usually transient. No deaths were directly related to hepatic decompensation in patients without pre-existing liver disease[10].

Most studies have addressed the prevalence of ALI and its association with clinical outcomes in patients hospitalized for COVID-19 pneumonia. However, few studies have focused on ALI's natural history and consequences in patients with mild COVID-19 or asymptomatic carriers. Only one SARS-CoV-2 infection without respiratory symptoms presenting with acute hepatitis has been previously reported in the literature[11]. Here, we report a case of COVID-19 presenting mild respiratory symptoms and inadvertently discovered elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels.

CASE PRESENTATION

Chief complaints

A 60-year-old woman was referred to the Department of Family Medicine of our hospital for further investigation of elevated liver enzymes during her health examination.

History of present illness

She was vaccinated three times (BNT162b2, Pfizer-BioNTech, New York, NY, United States) since the start of the COVID-19 pandemic and was infected with SARS-CoV-2 on July 12, 2022. After recovering from the infection, she underwent a health examination at our hospital on August 30, 2022. She recalled suffering only from a mild productive cough, without fever, chills, fatigue, or other discomforts. Hepatitis-associated symptoms were not observed, including nausea, vomiting, and changes in skin color, urine, or stool. There was no drug or alcohol abuse.

History of past illness

She had no remarkable medical history or chronic illness. Traditional Chinese medicine was self-administered for improved wellness during the past six months.

Personal and family history

There was no significant personal or family history.

Physical examination

There was no significant finding of physical examination.

Laboratory examinations

Laboratory blood liver function test revealed elevated AST level of 207 U/L (normal value < 39, UNL > 5.3) and ALT level of 570 U/L (normal value < 52, UNL > 10.9). Serum total bilirubin (TBI), alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT) levels were not elevated. There was no evidence of acute or chronic hepatitis A, B, and C (Table 1).

Imaging examinations

Abdominal ultrasound showed a calcified nodule in the liver (Figure 1), with no severe abnormalities in the liver, gallbladder, or other abdominal viscera.

FINAL DIAGNOSIS

The patient was diagnosed as ALI after mild COVID-19.

TREATMENT

The patient was treated as expectant management. No medication was prescribed.

OUTCOME AND FOLLOW-UP

ALI was closely monitored for asymptomatic features and an unknown etiology. The following week, blood tests showed a reduction in both AST and ALT levels (ALT 124 U/L, AST 318 U/L). Two weeks later, they had decreased to near the expected UNL (ALT 40 U/L, AST 76 U/L) (Figure 2).

DISCUSSION

Our case highlights the importance of monitoring unusual liver injury after mild COVID-19. We demonstrated that recovery from liver injury could be achieved by natural course. No medication or intervention was applied in this case.

Gastrointestinal (GI) symptoms associated with COVID-19 include diarrhea, vomiting, nausea, and decreased appetite[12,13]. The coronavirus infection in the intestinal tissue causes these GI symptoms [12]. Additionally, gut-brain interaction might also induce GI tract discomfort[13]. The complete blood count (CBC) in most SARS-CoV-2-infected patients with liver injury shows erythrocytes, platelets, and leukocytes within normal limits[13]. Our patient showed the same CBC pattern.

Patients with COVID-19 usually present elevated liver enzymes in liver function tests, including ALT and AST. However, severe liver injury is uncommon, even in severe COVID-19 cases[13]. SARS-CoV-2 enters the cells *via* the angiotensin-converting enzyme 2 (ACE2) receptor[14]. Cholangiocytes express the ACE2 receptor and may be invaded by SARS-CoV-2, causing elevated GGT[15]. Our patient also presented elevated GGT initially, decreasing after day 59. A previous study also showed hypoalbuminemia and elevated AST levels in critical COVID-19 cases[13]. It was suggested that albumin and AST could be liver function biomarkers in patients with COVID-19. AST elevation was noted in the case presented here, but no hypoalbuminemia was detected.

The mechanism by which COVID-19 triggers acute hepatitis still remains unclear. Sun *et al*[10] suggested several possible explanations, such as the combination of the immune-mediated inflammatory response, direct cytotoxic injury due to viral replication, hypoxic hepatitis, drug-induced liver injury, or reactivation of pre-existing liver disease. ACE2 expression in the biliary and hepatic endothelial cells can explain the observed liver injury[16]. Hypoxia, drugs, or pre-existing liver disease were disregarded in our case because of the patient's narrative history.

The molecular biology behind hepatic impairment is currently being explored since researchers are starting to recognize that ALI emerges as a clinically significant consequence of COVID-19. The hyperinflammation resulting from the cytokine storm and immune dysfunction provoked by COVID-19 contributes to ALI[17,18]. Pathological evidence of typical viral infection lesions with scarce $CD4^+$ and $CD8^+$ lymphocytes indicates that SARS-CoV-2 directly infects the liver[19]. Moreover, others believe that the virus binds to ACE2-positive cholangiocytes, not hepatocytes, and that cholangiocyte dysfunction induces liver injury[16].

COVID-19-induced liver injury may indicate that SARS-CoV-2 infection could cause multiple organ dysfunction. A previous pathological study of liver injury in a patient with COVID-19 showed mild lobular and portal activity and moderate steatosis[20]. Regarding imaging, computed tomography (CT) scans show typical liver injury characteristics in COVID-19 patients, including liver hypodensity and

Table 1 Laboratory test results

	Normal value	Day 39	Day 45	Day 59	Day 94
ALP	34-104 IU/L	87.00	88	80	79
AST (GOT)	40-124 U/L	207.00	124	40	24
ALT (GPT)	7-52 U/L	570.00	318	76	33
TBI	0.3-1.0 mg/dL	1.00	0.8	0.6	0.6
DBI	< 0.2 mg/dL	0.20	0.2	0.1	0.1
GGT	9-64 U/L	84.00	68	57	47
TP	6.4-8.9 g/dL	7.50			
ALB	3.5-5.7 g/dL	4.60			
GLO		2.90			
A/G ratio		1.60			
BUN	7-25 mg/dL	8.00			
UA	2.3-6.6 mg/dL	6.70			
CRE	0.6-1.2 mg/dL	0.67			
eGFR	> 90	95.40			
TCH	< 200 mg/dL	200.00			
TG	< 150 mg/dL	84.00			
GLU-AC	70-100 mg/dL	82.00			
Na	136-145 mmol/L	139.00			
K	3.5-5.1 mmol/L	3.70			
Ca	2.2-2.6 mmol/L	2.40			
HDL	> 50 mg/dL	47.00			
HbA1c	4%-6%	6.00			
eA GLU	mg/dL	125.00			
LDL	< 100 mg/dL	143.00			
Anti-mitochondria Ab	< 1:20		Negative		
HAV IgM		Negative			
Anti-HAV		Reactive			
HBs Ag		Nonreactive			
Anti-HBs		Negative			
Anti-HCV		Nonreactive			
AFP	< 9 ng/mL	1.30			
CEA	< 3 ng/mL	2.90			
FT4	0.59-1.43 ng/mL	1.29			
T3	72-172 ng/mL	130.00			
TSH	0.38-5.33 uIU/mL	1.41			
CA125	< 35 U/mL	4.20			
CA19-9	< 35 U/mL	2.40			
ESR	< 20 mm/h	28.00			
WBC	3.5-11.0× 10^3/μL	4.90			
RBC	4.0-5.2 × 10^3/μL	4.73			
PLT	150-400 × 10^3/μL	208.00			

ALP: Alkaline phosphatase; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; TBI: Total bilirubin; DBI: Direct bilirubin; TP: Total protein; ALB: Albumin; GLO: Globulin; A/G ratio: Albumin/globulin ratio; UA: Uric acid; CRE: Creatinine; eGFR: Estimated glomerular filtration rate; TCH: Total cholesterol; TG: Triglyceride; GLU-AC: Glucose before the meal; GGT: Gamma glutamyl transpeptidase; Na: Sodium; K: Potassium; Ca: Calcium; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; HAV: Hepatitis A virus; HBs: Hepatitis B surface antigen; HCV: Hepatitis C virus; AFP: Alpha fetal protein; CEA: Cancer embryonic antigen; FT4: Free thyroxin; T3: Triiodothyronine; TSH: Thyroid-stimuating hormone; CA: Carbohydrate antigen; ESR: Erythrocyte sedimentation rate; WBC: White blood cells; RBC: Red blood cells; PLT: Platelet.

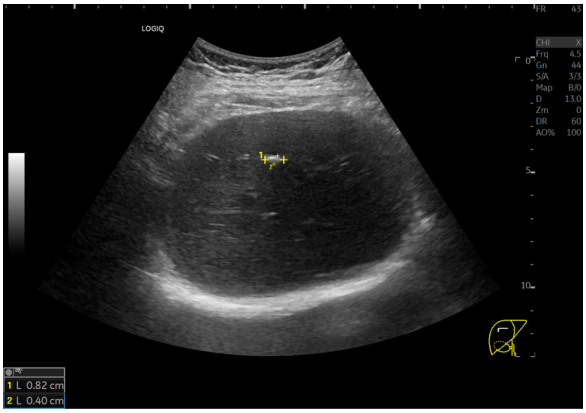

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Figure 1 Abdominal ultrasound showing a calcified nodule in the liver (measure mark). No liver hypodensity and pericholecystic fat stranding were noted.

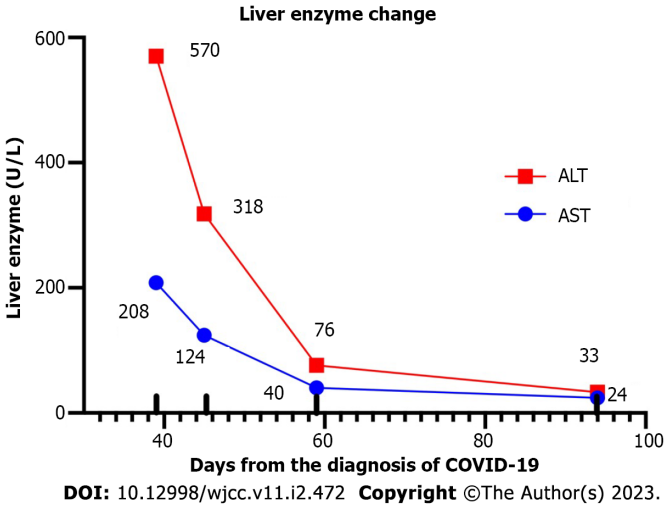

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Figure 2 Trend in alanine aminotransferase and aspartate aminotransferase levels after coronavirus disease 2019 diagnosis (on days 39, 45, 59, and 94). The liver enzymes returned to normal values after 94 d of coronavirus disease 2019. AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; COVID-19: Coronavirus disease 2019.

pericholecystic fat stranding[13]. Findings of liver hypodensity in imaging may also indicate liver steatosis[13]. Unfortunately, in our case, a liver CT scan was not performed due to the patient's mild symptoms.

Severe COVID-19 correlates with severe hepatic, renal, cardiovascular, and coagulation complications [9]. Liver injury is an independent predictor of severe COVID-19 and even hospitalization and death in critically ill COVID-19 patients[21]. Our case illustrates that patients with mild COVID-19 could present variable degrees of organ impairment. These events may be subclinical and not anticipated solely by the severity of COVID-19. Thus, prompt surveillance and special care should be provided to treat these patients, and long-term outcomes should be monitored. Fortunately, COVID-19-related ALI has been reported to be self-limiting, and the outcomes have been satisfactory. The long-term effects on liver function remain unclear[10].

Previous studies documented that an active lifestyle[22] and healthy dietary patterns[23] may decrease the COVID-19 severity. There was no information about these confounding factors in the current case study.

CONCLUSION

This case report describes a patient with mild COVID-19 complicated by acute liver injury. This case is noteworthy because substantially elevated aminotransferase levels were discovered in a mild COVID-19 case, proving that not only patients with severe disease can develop ALI. Clinicians should pay attention to liver function testing during the COVID-19 treatment regardless of disease severity. Patients with similar characteristics should be identified to establish clinical significance and treatment principles and provide information to determine the, still unclear, long-term impact of COVID-19 on liver function.

FOOTNOTES

Author contributions: Ding DC and Lai PH conceptualized the study; Lai PH contributed to data curation; Ding DC and Lai PH wrote the original draft; Ding DC and Lai PH were involved in writing and review.

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LETTER TO THE EDITOR

Incidence and clinical treatment of hypertriglyceridemic acute pancreatitis: A few issues

Qun-Ying Yang, Qian Zhao, Jian-Wen Hu

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Abstract

Hypertriglyceridemia is a well-recognized etiology of acute pancreatitis, and the incidence of hypertriglyceridemic acute pancreatitis (HTG-AP) has increased in frequency worldwide in response to lifestyle changes. It is crucial to identify hypertriglyceridemia as the cause of pancreatitis and initiate appropriate treatment. Insulin treatment produces effective lowering of triglycerides, but in our opinion, non-diabetic patients with HTG-AP require separate consideration to avoid hypoglycemia.

Key Words: Hypertriglyceridemic acute pancreatitis; Incidence; Etiology; Insulin; Treatment

Core Tip: This is a comment on an article concerning the incidence and clinical characteristics of hypertriglyceridemic acute pancreatitis (HTG-AP). We believe that the risk of hypoglycemia must be considered and described for non-diabetic patients with HTG-AP receiving insulin infusion to decrease serum triglyceride level.

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TO THE EDITOR

We read with great interest the article published by Lin *et al*[1], which retrospectively analyzed the incidence and clinical characteristics of 371 patients with hypertriglyceridemic acute pancreatitis (HTG-AP) in their hospital over the past 10 years. This is worth paying more attention to, as HTG-AP is often associated with persistent organ failure and a poor prognosis[2]. The authors concluded that the incidence of HTG-AP was significant increase and patients with mild and moderately severe acute pancreatitis can be treated with insulin safely and effectively. However, in our opinion, there are several viewpoints in this study that merit further discussion.

First, the Introduction section states that the incidence and mortality of HTG-AP have surpassed alcohol to become the second leading cause of AP in China. It is worth reflecting on this statement further. This viewpoint contradicts the conclusions of its cited reference[3] in the article, which concludes that hypertriglyceridemia is a relatively uncommon (9%) cause of AP, but that patients with hypertriglyceridemia have a high (14%) incidence of AP. The reference does not support their viewpoint.

Second, the majority of recent studies indicate that hypertriglyceridemia is the third most common etiology of AP, secondary to gallstones and alcohol abuse[4-6]. A multicenter 5-year study[7] on the etiology of AP in Beijing found that alcoholic and HTG-AP were higher in patients below 50 years and biliary pancreatitis was higher in patients over 70 years, so we think that the etiology of AP may differ according to age, sex, and severity. The morbidity of HTG-AP has increased at a fast rate in recent years, but its ranking is controversial.

Third, the Results section states that the serum triglyceride (TG) levels of patients with mild and moderately severe AP significantly decreased by intravenous insulin without hemoperfusion. However, we believe further explanation regarding the method and safety of intravenous insulin is necessary. There are no current guidelines for the management of HTG-AP, although the rapid reduction of TG level is considered an important therapeutic goal. Insulin, heparin, plasma exchange, and hemoperfusion are the most frequently reported therapies[8-11]. Insulin has been deemed the sole hypoglycemic hormone in mammals since its discovery in 1921. Continuous administration of exogenous insulin achieved normoglycemia and corrected severe hypertriglyceridemia in all patients with type 2 diabetes presenting with severe hypertriglyceridemia and hyperglycemia[12]. However, the risk of hypoglycemia for non-diabetic patients needs to be considered, and appropriate insulin infusion doses, frequent blood glucose checks, and concomitant glucose infusion implemented are needed. The current available literature on this topic are scarce and largely consist of single case report; empirical initiation of a higher dextrose concentration infusion with glucose level titrations should be considered to avoid hypoglycemia[13,14].

Fourth, we agree with this statement that increased TG levels directly affected the determination of amylase. Spuriously, low plasma amylase has been noticed in presence of lactescent plasma, which affects the expression of biomarkers used for the follow-up of the acute pancreatitis episode[15].Visual examination of plasma represents a simple clinical sign, allowing the identification of severe hypertriglyceridemia at low cost.

In the end, this observational study can provide a reference for clinical practice, but the number of cases used for propensity score matching was relatively small, which possibly affected the statistical power. We believe that the diagnosis rate and therapeutic efficacy of HTG-AP merit further studies.

FOOTNOTES

Author contributions: Yang QY and Zhao Q reviewed the literature and contributed to manuscript drafting; Hu JW was responsible for the revision of the manuscript for important intellectual content; All authors reviewed and approved the final version.

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LETTER TO THE EDITOR

Management of infected acute necrotizing pancreatitis

Efstathios T Pavlidis, Theodoros E Pavlidis

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Abstract

Necrotizing or severe pancreatitis represents approximately 10%-20% of acute pancreatitis. 30%-40% of patients with acute necrotizing pancreatitis (ANP) will develop debris infection through translocation of intestinal microbial flora. Infected ANP constitutes a serious clinical condition and is complicated by severe sepsis with high mortality rates of up to 40% despite progress in current intensive care. The timely detection of sepsis is crucial. The Quick Sequential Organ Failure Assessment score, procalcitonin levels > 1.8 ng/mL and increased lactates > 2 mmol/L (> 18 mg/dL), indicate the need for urgent management. The escalated step-by-step management protocol starts with broad-spectrum antibiotics, percutaneous drainage or endoscopic management, and ends with surgical management if needed. The latter includes necrosectomy (either laparoscopic or traditional open surgery), peritoneal lavage and extensive drainage. This management protocol increases the chance of survival to approximately 60% in patients with otherwise fatal cases. Any treatment choice must be individualized, and the timing is critical.

Key Words: Pancreas; Acute abdomen; Acute pancreatitis; Necrotizing pancreatitis; Sepsis; Septic shock

Core Tip: Infected acute necrotizing pancreatitis requires multidisciplinary management and multiple interventions that must be individualized. Early recognition of sepsis and prompt step-by-step individualized management for timely debridement and intensive care are imperative to improve outcomes.

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TO THE EDITOR

We read with great interest the recent paper by Xiao *et al*[1], and we would like to express our satisfaction and congratulations for their excellent work. It is a well-written comprehensive opinion review presenting the current data on the serious condition of infected necrotizing pancreatitis (INP). I agree absolutely with the proposed step-by-step management. We would like to reiterate that the timely detection of sepsis is crucial. Despite intensive care efforts, ongoing deterioration of the clinical picture is a strong indicator of great relevance, especially during the first 7-14 d from the onset of acute pancreatitis. The Quick Sequential Organ Failure Assessment score (at least two of the following three clinical indications are present: Tachypnea ≥ 22/min, low level of consciousness, and arterial pressure ≤ 100 mmHg) for sepsis is a bedside prompt for identifying patients with suspected severe infections and poor outcomes[2]. Therefore, it has significant value for treatment decision-making when facing INP[3].

The necrotizing form represents approximately 10%-20% of patients with acute pancreatitis, with an overall mortality of up to 15%[3,4]. However, 30%-40% of patients with acute necrotizing pancreatitis (ANP) will develop debris infection through translocation of intestinal microbial flora. Infected ANP is complicated by severe sepsis, with high mortality rates up to 40% despite progress in current intensive care[2,5,6]. The escalated step-by-step management consists of endoscopic management, interventional methods and surgical approaches. The timing of interventional application is still under debate[1,3,4,6]. However, early recognition and timely debridement are crucial. Thus, reliable predictive factors of infected debris are essential for proper management of high-risk and potentially fatal cases[5,7].

C-reactive protein (CRP) levels above 150 mg/dL predict severe ANP on admission. Procalcitonin (PCT) above 0.5 ng/mL is a predictor of ANP from the first twenty-four hours. Serial assessment of changes in PCT reflects the course of the disease. Levels above 1.8 ng/mL are an indication of infected ANP[5]. Lactate levels greater than 2 mmol/L (> 18 mg/dL) indicate severe sepsis[2].

An Acute Physiology and Chronic Health Evaluation II score ≥ 14 on admission, early persistent systemic inflammatory response syndrome (SIRS) within the first forty-eight hours and multiple organ dysfunction syndrome (MODS) within two weeks after admission constitute prognostic factors of higher mortality after operative necrosectomy[5].

A predictive model, based on CRP, albumin, creatinine and alcohol abuse as the etiology of acute pancreatitis, has been developed for the distinction of infected and noninfected ANP[7]. Microbial culture and metagenomic next-generation sequencing of pancreatic fluid aspirate under computed tomography (CT) guidance have been proposed for a more accurate and timely diagnosis of a suspected ANP infection[8]. Obesity [body mass index (BMI) > 30] has a negative effect on both the development and course of ANP. The possibility of infected ANP and MODS is higher in obese individuals than in nonobese individuals, and early interventional drainage is required. Increased mortality is associated with increasing BMI[9].

The immune response that is expressed by an early increase in anti-inflammatory cytokines [tumor necrosis factor (TNF) soluble receptors, interleukins (IL)-10, IL-1 receptor antagonist] is of great research interest[5]. Another interesting predictive novel biomarker of ANP is the gut microbiome on admission. *Enterococcus faesium* and *Finegolbia magna* have been postulated as potential predictors of NP and INP [10]. Infected ANP is indicated by the presence of extraluminal peripancreatic gas bubbles on imaging and can be confirmed by positive microbial culture on fine needle aspiration by imaging guidance. However, the latter has been used less often in clinical practice[3]. The step-by-step management protocol starts with broad-spectrum antibiotics, percutaneous drainage or endoscopic management, and ends with surgical management if needed[3,11].

Ultrasound-guided percutaneous management, either transgastric or transabdominal drainage, for infected fluid collections is the first-choice method, with success rates ranging between 50% and 75%[12-14]. Transgastric debridement and drainage are not technically applicable early within the first 2-4 wk before the cyst wall matures, in lesser sac locations or in walled-off cysts at distant sites from the stomach. Transabdominal drainage is an alternative option for sepsis control[4]. For fluid removal and debridement, adequate drain placement is needed. Double pig-tail plastic stents or esophageal fully covered self-expandable metal stents have been used[4,11,15-17]. Percutaneous direct endoscopic necrosectomy is feasible despite technical difficulties, but the technique requires relevant experience[4]. Failure of the procedure ultimately requires surgical necrosectomy[3,18]. A randomized study of long-term follow-up showed that there was no superiority of endoscopic over surgical management in terms of major complications and mortality in infected ANP. The only difference found in favor of endoscopy was fewer pancreatic fistulas requiring reoperation[19].

Laparoscopic management of infected pancreatic necrosis or peripancreatic infected fluid collection is feasible, safe and effective; it encompasses extensive necrosectomy, detailed irrigation of the peritoneal cavity (lavage) and placement of drain catheters. The retroperitoneal approach is another alternative access route[20]. Indocyanine green-guided video-assisted retroperitoneal debridement has been used for clear surface separation of debris in the management of infected ANP. This method is safe and avoids the risk of vascular and healthy pancreatic parenchymal injury resulting in persistent fistula[21].

Traditional open surgical debridement, irrigation and drains, leaving open the abdomen (for example, vacuum-assisted closure) for planned reinterventions have been limited to critically ill patients [3]. The novel effective application of nanotechnology in diagnosis and treatment is a promising evolution[22]. Serum pancreatic enzyme assessment and imaging for early detection of the disease course may be useful. Nanoparticles have been used as drug carriers and could be valuable for the application of both antibodies and antibiotics. Nanotechnology could be used to possibly overcome the resistance of microbes to antibiotics. In addition, it has been postulated that gene therapy may be more effective than drug therapy in severe acute pancreatitis[22].

In addition to what has already been mentioned above, novel future directions include nanotechnology, the application of hydrogen peroxide (H_2O_2) in necrosectomy, 3-dimensional CT (3D CT) cinematic, and anti-inflammatory monoclonal antibodies. The preliminary use of H_2O_2 in endoscopic necrosectomy of walled-off necrosis showed excellent outcomes. Thus, prospective randomized controlled trials are necessary to precisely establish its role[23,24].

The novel volumetric 3D CT and cinematic rendering may improve further diagnosis and prognosis by precisely identifying infected necrotic tissue and local complications[25]. To date, there has not been etiopathogenic management of severe sepsis and septic shock consequences, despite the current considerable progress, unless patients undergo surgery and supportive intensive care. In infected pancreatic necrosis, proinflammatory factors, mainly TNF-α but also IL-6, IL-8 and monocyte chemotactic protein, activate the body's defense response to inflammation, causing SIRS, which is called sepsis. If this initially beneficial reaction is not balanced by the compensatory anti-inflammatory response syndrome, then it will become uncontrolled and excessive, which leads to disseminated cell damage causing MODS and ultimately death[22,26]. Thus, the regulation of this balance by the use of antibodies or molecules against the most important inflammatory mediator of the cytokine cascade, TNF-α, would be crucial. The levels of TNF-α were increased within 1-2 h of endotoxin injection in an experimental model[26].

In conclusion, the current step-by-step, timely and individualized management of infected ANP is essential and improves patient outcomes. Percutaneous catheter drainage is the first step. Endoscopic debridement usually requires an elapsed time of three to four weeks. Transgastric debridement (laparoscopic or open) is suitable for central retrogastric collections. Laparoscopic transperitoneal debridement is suitable for isolated collections at the root of the mesentery. Open transperitoneal debridement is only performed when a collection is inaccessible to all other methods of drainage or after the step-up approach has failed.

FOOTNOTES

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