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REVIEW

Progress in sensorimotor rehabilitative physical therapy programs for stroke patients

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Abstract

Impaired motor and functional activity following stroke often has negative impacts on the patient, the family and society. The available rehabilitation programs for stroke patients are reviewed. Conventional rehabilitation strategies (Bobath, Brunnstrom, proprioception neuromuscular facilitation, motor relearning and function-based principles) are the mainstream tactics in clinical practices. Numerous advanced strategies for sensory-motor functional enhancement, including electrical stimulation, electromyographic biofeedback, constraint-induced movement therapy, robotics-aided systems, virtual reality, intermittent compression, partial body weight supported treadmill training and thermal stimulation, are being developed and incorporated into conventional rehabilitation programs. The concept of combining valuable rehabilitative procedures into "a training package", based on the patient's functional status during different recovery phases after stroke is proposed. Integrated sensorimotor rehabilitation programs with appropriate temporal arrangements might provide great functional benefits for stroke patients.

Key words: Stroke; Rehabilitation; Sensory stimulation; Thermal stimulation

Core tip: Rehabilitation strategies, including conventional interventions with an empirical basis and advanced interventions based on scientific evidence, are reviewed. The concept of a training package that is related to the severity of impairment and the phase of recovery from stroke is proposed to maximize the recovery of motor function after a stroke. The training package for therapists provides valuable suggestions for selecting from the available and suitable advanced rehabilitation methods as well as from the conventional rehabilitation methods.

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INTRODUCTION

Following stroke, more than half of the patients have moderate to severe deficits at admission, and their functional activities are often confined to the bedside or wheelchair[1,2]. The most commonly occurring deficits are hemiparesis, resulting in an immediate impairment to upper limb function[2-4], or the ability to stand, balance and walk[2,3,5]. These deficits not only limit the person's activities in the family and participation in society but pose a heavy physical burden on their relatives or caregivers[6]. Stroke patients recover their walking function to a certain degree after discharge from hospital. However, 50% or more of stroke patients are still frustrated by mild or severe deficits of their upper limb functions 6 mo post-

stroke[2-5]. Thus, facilitating the restoration of upper limb motor function and maximizing walking ability as early as possible after a stroke are generally priorities for stroke patients, their families and clinicians.

In the clinic, numerous rehabilitative approaches have been shown to promote functional motor recovery after stroke[7-14]. In general, repetitive sensory stimulation and mass motor or task practice facilitate neuroplasticity and brain reorganization in stroke patients, resulting in enhanced motor and functional recovery after stroke[13-17]. In this scenario, physical therapy that emphasizes sensory stimulation has gained increased prominence among modern rehabilitation strategies[13-16]. However, there has been no systematic review of sensorimotor rehabilitation programs according to the patient's status during different stroke rehabilitation phases (the acute, subacute and chronic phases). Due to the dynamic and complex process of stroke recovery (the patient's status and recovery phase)[10,11] and the methodological heterogeneity in various studies[7-10], it is difficult to draw a conclusion as to which programs are superior to others or which ones could be adopted for the entire rehabilitation process. In this article, we attempt to summarize all of the possible programs and introduce a schematic program that combines valuable treatments[9,11] into "a training package" to maximize the functional outcomes of stroke patients.

CATEGORIZATION OF STROKE REHABILITATION PROGRAMS

Regarding physical therapy for stroke patients, the rehabilitative programs can be categorized into two main groups according to the theoretical backgrounds of the clinical trials[7-14]: conventional and advanced rehabilitation programs.

Conventional rehabilitation programs address the effectiveness of treatment approaches based on neurophysiological, motor control and learning, or strengthening and functional principles. These programs are often called traditional physiotherapeutic "schools"[7-9,13,14]. The present study considered conventional rehabilitation programs to be the regular or standard therapies applied in clinical stroke rehabilitation. Conventional rehabilitation strategies are mostly based on clinical experiences and observations[18-24]. They were developed early and are usually applied for routine rehabilitation in the clinic.

Advanced rehabilitation programs emphasize the effectiveness of specific interventions based on neuroscientific evidence[7-14]. Because stroke patients must receive a reasonable level of rehabilitation in the hospital, conventional rehabilitation strategies are generally employed in the clinic. There is concern over incorporating advanced rehabilitation strategies with conventional rehabilitation strategies in the hospital due to ethical issues. In particular, in the case of acute and subacute stroke patients, the assessment for advanced rehabilitation yields two groups: a conventional + advanced rehabilitation group *vs* a conventional rehabilitation group. Only a few studies in chronic stroke patients have directly compared the advanced treatment with "dose-matched" conventional rehabilitation.

CONVENTIONAL REHABILITATION STRATEGIES

The conventional rehabilitation strategies for stroke include the Bobath (also called Neurodevelopmental Treatment)[14,18,19], Brunnstrom[20], proprioceptive neuromuscular facilitation (PNF)[21], motor relearning[22] and the functional or strengthening[7-9,13,14,23,24] approaches. Although these approaches are mostly based on empirical results rather than scientific evidence, they or their concepts are commonly adopted in clinical settings in the standard or routine rehabilitation programs for stroke patients to regain their motor functions[7-9,11-14].

In recent decades, several studies have shown the positive effects of these interventions on the recovery of motor functions after strokes[23-33]. Among these approaches, the Bobath treatment is widely used in Western countries[30-33]. Abnormal muscle tone and movement patterns, which generally lead to impaired postural control, are deemed the two major problems experienced by people with hemiplegia. Therefore, a major goal of the Bobath treatment[18,19] is to normalize the movement pattern and postural control (or tone) by handling the major joints of each body part of the patient, such as the neck, shoulder, hand, hip, knee and ankle. Recently, the Bobath treatment was re-defined as a problem-solving approach for the assessment and treatment of individuals with deficits in function, movement, and postural control caused by a central nervous system lesion. The goals in a given task are successfully met by identifying and analyzing problems in the movement components and the underlying impairments during functional activities and participation[19]. Incorporating appropriate inputs (visual, verbal, or tactile) also plays a vital role in Bobath training because the afferent inputs affect the motor performance[19]. The Bobath treatment should improve the efficiency of movement and generally facilitate the activities of everyday life.

The Brunnstrom approach[20] considers six hierarchical movement developmental stages, from flaccidity to normal movement-pattern control. The Brunnstrom treatment involves a reflex or limb synergistic movement, initially with cutaneous stimulation. Later, the appropriate inhibition of the synergy pattern and facilitation of the anti-synergy pattern are required to attain normal movement control and functional performance. Visual and somatic modalities are considered in the motor training using the Brunnstrom approach, which facilitates volitional movement and motor recovery for patients with moderate to severe strokes.

The PNF approach stresses stimulating proprioceptors in the muscles/joints of the affected limbs following stroke. The PNF procedures are often accompanied by verbal/visual and tactile feedback to facilitate muscle

Table 1 Summary of conventional rehabilitation therapies with an emphasis on sensory inputs and outcomes

Treatment	Sensory inputs	Rationale	Sensory outcome	Result[1]
Bobath	Visual, verbal and tactile	Neurophysiology concept (emphasis on selective movement and postural control by key points of the body, with problem-solving training)	None	UL (-), LL (-)
Brunnstrom	Visual and cutaneous	Neurophysiology (an ordered, predictable, stepwise progression from initial flaccidity to stereotypical synergy and then to normal patterns of voluntary movements)	None	NA
PNF	Visual, tactile, verbal and proprioceptive	Neurophysiology concept (through the stimulation or relaxation of muscle groups combined with various sensory inputs in response to specific movement patterns to promote functional movement)	None	NA
Motor relearning	Visual, tactile and auditory	Neuropsychology (Active practice of context-specific motor task with well-designed motor and sensory components)	None	NA [UL (-) and LL (-) motor control with 3 RCTs]

[1]Obtained from meta-analyses or systematic reviews. PNF: Proprioceptive neuromuscular facilitation; -: Not better than the control group; LL: Lower limb; UL: Upper limb; NA: Not available; RCT: Randomized clinical trial.

contraction and motor control in terms of many techniques, such as joint approximation, traction, irradiation or overflow. Therapists rebuild the movement and function of the limbs rendered paretic due to strokes by guiding a specific movement pattern (diagonal or spiral direction) for concomitant muscle contractions with reversal, stabilization, repetition or combination techniques. The motor control or movement pattern facilitated by the therapist follows a sequence of static/dynamic and assistive-active-resistant progressions for regaining motor control and enhancing the muscle strength of the paretic limbs of stroke patients. Verbal and vision inputs are also basic facilitative procedures used in this approach[21]. The facilitated progression due to the PNF procedures follows a hierarchical process from mobility to stability, then controlled mobility to skillful movement.

The motor relearning technique[22] emphasizes the active practice of context-specific motor tasks in a structured environment with appropriate feedback, manual guiding or verbal commands. Through this well-designed learning program, stroke patients progressively learn to perform the task-oriented functional activities well. In general, the motor relearning technique consists of the following four steps: (1) analysis of the task; (2) practicing the missing components of the task; (3) practicing the entire task; and (4) transferring the training to perform the task. This technique requires the patient to first understand the kinematics and kinetics of normal movement and then the patients can use the kinetic knowledge to practice various dynamic characteristics of the movements necessary to complete a task. The motor relearning technique recruits a single or several inputs (visual, verbal, or auditory) within a training program.

The functional and strengthening approaches, which are based on theories regarding motor control and learning, consist of bed mobility, sitting, transfers, sit-to-stand and gait[7-9,13]. Clinically, the therapists target the impairments in the neuromuscular or musculoskeletal system following stroke and provide practice or an experience leading to changes in the capability of producing skilled action. To reduce impairments and facilitate functioning, the therapists encourage the patients to practice purposeful or functional movement and postural adjustment by selective allocation of muscle tension across joint segments[7-9,13].

The aforementioned rehabilitation strategies are often used in a clinical setting for stroke patients, but the scientific evidence regarding these conventional rehabilitation methods remains limited. The functional outcomes of the Bobath and motor relearning approaches[25-27] were not significantly different throughout a 4-year follow-up[27], but the motor relearning treatment is seemly preferred for shortening the length of hospitalization of stroke patients during the acute phase. No significant difference was found in the functional outcomes of stroke patients given the Bobath, PNF, Brunnstrom and/or strengthening treatments[24,28,29]. Although the Bobath technique is more popular in Western countries[30,31], recent reviews indicated that the Bobath technique is not superior to the other approaches in general, including the outcomes regarding the sensorimotor control of upper and lower limbs, dexterity, mobility, the activities of daily living or the health-related quality of life[31-33]. Interestingly, a mixture of treatments combining different approaches may be more beneficial than receiving no treatment or a placebo control for lower limb functionality and postural control after strokes[8].

Table 1 summarizes the characteristics of the sensory inputs and outcomes, theoretical basis, and the results of the four conventional rehabilitative strategies. Due to the methodological heterogeneity in previous studies and the lack of well-designed larger investigations, the ideal and favorable training strategies among these conventional treatments for stroke rehabilitation are yet to be determined[19-23].

ADVANCED REHABILITATION STRATEGIES

Numerous advanced and novel rehabilitation treatments have been developed for patients in the acute, subacute or chronic phase of stroke, to facilitate and maximize their functional recovery[7-14]. Most of these techniques are

based on neuroscientific evidence rather than pragmatism. For instance, neuroplasticity and brain reorganization in patients with good functional recovery from strokes have been demonstrated using functional brain imaging or other advanced neuro-technologies[8-11,15,16]. Compared to conventional rehabilitation treatments, more high-quality clinical trials concerning the advanced rehabilitation strategies have been reported in recent decades. In this study, several advanced rehabilitation techniques and their enhanced results compared with those of conventional rehabilitation treatment are summarized below.

ELECTRICAL STIMULATION

Electrical stimulation (ES) is a technique that was developed early and is widely applied to stroke rehabilitation as an adjunctive treatment[7-10,17,34-44]. Many aspects of ES, including transcutaneous electrical nerve stimulation (TENS)[34-38], functional electrical stimulation (FES) or neuromuscular electrical stimulation (NMES)[14-17,34,37-40,44], and electromyographic (EMG) biofeedback[41-43], have been used for different clinical purposes. TENS is generally applied for sensory stimulation (sensory threshold) or for selective muscle contraction (motor threshold) based on the patient's status[35-38]. In contrast, the intensities of the other three modalities are largely above the motor threshold[34,37-44]. ES primarily stimulates cutaneous receptors and proprioceptors and/or activates muscle contractions and joint movements, which can increase the cortical excitability of the somatosensory and/or motor areas. Long-lasting cortical plasticity occurs, accompanied by motor recovery, in stroke patients treated by ES[13-17,36]. ES is popularly used as an adjunct in clinical rehabilitations and has a positive effect on the range of motion, motor control, and muscle strength of the affected limbs and the gait speed of stroke patients[13-16,34-43]. The ES intensity with sensory threshold shows effects on motor outcomes[16,37]. In particular, ES combined with active training significantly improved the performance of both sensory and motor functions[34,36]. In addition, ES may also be beneficial in preventing secondary complications of stroke[39], such as shoulder pain, subluxation, spasticity and upper limb contracture.

The EMG biofeedback technique, another type of ES involving minimally active muscle contraction at the targeted joint, is also beneficial for the control of motor function or the muscle strength of the upper limb following stroke[41-43]. However, the EMG-triggered feedback causes little improvement in upper limb functionality[43]. The effect of the NMES with three periods of stimulation on the upper extremities of 66 stroke survivors with severe motor deficits was investigated[44]. However, the optimal effective parameters of ES are inconclusive[36,37]. The ES treatments used in all of the previous studies have been added to conventional rehabilitation programs to enhance motor-function recovery after a stroke[34-38,40-44].

ROBOTIC-AIDED SYSTEMS

The most advantageous feature of robotic-aided system is that it reduces the physical effort of handling patients using computer-assisted devices. Because the system can automatically set the duration and intensity of the paretic limb movement using either passive or active assistance, robotic-aided therapy allows patients to train independently with no therapist or with a supervising therapist[45,46]. The device may provide different optimized movement patterns to help moderate to severe stroke patients regain their motor functions. However, a robotic-aided system requires that the distal part of the limb (hand or foot) be fixed on the handle bar or footplate of the device during training.

At least five types of robotic-aided systems have been developed for upper limb rehabilitation after a stroke, including the MIT-MANUS, the InMotion shoulder-elbow robot, the ARM Guide, the mirror-image motion enabler, and the bi-manu-track[45-50]. Generally, the exercise protocols of a robotic therapy system for upper limb rehabilitation after a stroke focus on shoulder and elbow movement patterns and fixing the hand (or fingers) in the robotic handle bar[44-48]. The system guides a patient's paretic hand on a support board in front of the patient and tracks the movement of the robotic handle to the target on the computer screen to attain a goal-directed movement through simultaneous visual, auditory, and proprioceptive feedback. Robotic-aided therapy has demonstrated advantages for motor recovery but did not affect the daily functions of stroke patients[46]. However, when directly compared with matched intensive conventional rehabilitative techniques, the robot-assisted therapy showed no additional benefit for moderate to severe arm impairment in subacute stroke patients[47].

The Lokomat and Gait Trainer were recently developed as robotic-gait machines for lower limb rehabilitation following stroke and are intended to relieve the strenuous efforts of the therapists[51-53]. Although their effects were not significantly different compared with those of a similar dosage of treadmill training[51] or conventional therapy[52], using the robotic-gait machine is a feasible treatment for lower limb and gait rehabilitation[51-53]. Robotic-gait therapy combined with conventional therapy is more effective for gait performance than conventional therapy alone in patients with subacute stroke who have greater motor impairment[53]. A similar phenomenon regarding better improvement has been reported for using robotic-gait therapy combined with FES treatment[54].

The use of a robotic-aided system for stroke rehabilitation is rapidly growing. Recently, robotic-aided therapy combined with individual arm therapy (IAT) using a motor relearning approach was as effective as double sessions of IAT in terms of the restoration of upper limb motor functions[47]. Robot-assisted therapy during the training phase is more convenient than conventional rehabilitation therapy. However, the cost of the devices is still prohibitive for the average clinic[52].

PARTIAL BODY WEIGHT SUPPORTED TREADMILL TRAINING

Partial body weight supported treadmill training (PBWSTT)

involves using a treadmill with body-weight support provided by a harness that is connected to an overhead support system, with coincidental proprioceptive stimulation and visual inflow during stepping. PBWSTT is a method used to treat walking impairments post-stroke. PBWSTT has been used for more than 20 years and is beneficial for the walking function of stroke patients[55-60]. Initially, the stroke subjects in most of the previous PBWSTT studies were independent or partially independent walkers and many of the studies were conducted using chronic stroke patients[55-57]. These studies reported a good outcome after the application of the PBWSTT. In contrast, the outcomes of early severe stroke patients or even patients after a 6-mo follow-up compared with those given conventional rehabilitation training are controversial[57,58]. In a large long-term follow-up study, the effects of PBWSTT were not superior to progressive exercise at home that was managed by a physical therapist[59]. The use of PBWSTT for walking rehabilitation of stroke patients slightly improved the walking velocity and walking endurance but not significantly compared with the effects of conventional rehabilitation[60]. Moreover, two (or even three) therapists and a strenuous effort are generally required during PBWSTT therapy. Thus, these factors could limit clinical therapists from initiating walking training on the treadmill to moderate to severe stroke patients in the acute phase.

VIRTUAL REALITY

Computerized virtual reality (VR), a type of human-computer interface technology, allows patients to interact with a multisensory simulated environment and to receive "real-time" feedback on their performance[61,62]. Visual and auditory feedback is crucial for instantaneous reactions to stimulation from the environment or the exercises. The feedback training incorporated with conventional rehabilitation treatment led to significant improvement of the upper arm functions of stroke patients[61,62].

VR applications can range from nonimmersive to fully immersive. Recently, a variety of nonimmersive video game systems developed by the entertainment industry have become available for home use. The home-based VR system is inexpensive and more accessible to clinicians and individuals. Among patients with acute strokes who were receiving conventional rehabilitation, the group receiving VR therapy using Wii games demonstrated better recovery of motor function than the recreational group[63]. Furthermore, VR therapy in conjunction with PBWSTT treatment is feasible and effective in improving patients' walking and balancing abilities post-stroke[64].

Although VR can enhance patients' motivation and compliance regarding rehabilitation and reduce their perception of exertion during activities, it is unable to replace actual sensory experiences, such as manipulating objects during normal daily activities. Sometimes, the VR system may cause symptoms of motion sickness, such as nausea, disorientation, dizziness, and headache, in a few patients during training[61]. A recent review[62] summarized the results of five randomized clinical trials (RCTs) and seven observational studies, concluding that large multicenter, well-designed randomized trials of VR therapy are required. However, the subjects enrolled in most VR studies have a moderate to mild status, which limits the apparatus to a selected group of stroke patients. The cost and complexity of VR devices and the supporting software may not be acceptable for all clinical centers.

INTERMITTENT COMPRESSION

The intermittent compression technique is a neurophysiological treatment. This treatment involves the stimulation of cutaneous and proprioceptive receptors by repeated movements. Previous randomized control trials have shown its beneficial effects on the sensory and motor functions of stroke patients in the acute[65] or chronic[66] phase. A significant enhancement was observed in subjects even at the 5-year follow-up[67]. However, heretofore, no further investigations have been conducted.

CONSTRAINT-INDUCED MOVEMENT THERAPY

Constraint-induced movement therapy (CIMT) is a revolutionary rehabilitation technique based on the "learned non-use" theory[68-73]. The concept of CIMT involves constraining the movements of the non-affected arm with a sling or mitten and forcing the paretic hand to practice using a task-orientated approach for most of the waking hours. Highly intensive and mass-repetitive practice using the affected arm is the major requirement for at least 2 wk of training. Two mechanisms underlying CIMT were proposed[71,73]: the "learned non-use" of the affected limb, which is often behaviorally reinforced, is reversed and the contralateral cortical area responsible for the movement of the affected limb is expanded due to repetitive forced use[69]. Although CIMT therapy has been proven to have a significant effect on the upper limb mobility following strokes[68-73], a minimal voluntary movement (wrist extension of at least 20 degrees and finger flexion of 10 degrees) at the beginning of treatment and during long-duration daily treatment is required for the application of this therapy. Thus, it is uncertain whether the CIMT approach is appropriate for patients with flaccidity or little volitional movement of their upper limbs during either the early or chronic phase of stroke and those with insufficient tolerance of the method. In the case of mild motor function in chronic stroke patients[71,73], CIMT therapy could act as a routine rehabilitation technique.

THERMAL STIMULATION

Thermal stimulation (TS) was first developed using alternative hot and cold stimulation. TS combined with conventional rehabilitation methods has been demonstrated to facilitate upper-limb motor function in acute stroke patients[74]. TS causes greater activation of the brain areas

Table 2 Comparison of the characteristics of sensory stimulation modalities and the rationales for recent advanced rehabilitation strategies and their outcomes

Treatment	Sensory modality	Rationale	Sensory outcome	Result[1]
Electrical stimulation	Proprioceptive and tactile	Neurophysiology/neuropsychology	Yes (+)	UL (+) for motor control, LL (+) for gait ability
Robotic therapy	Visual, auditory and proprioceptive	Neurophysiology/neuropsychology	None	UL (+) for motor control
Virtual reality	Visual and auditory	Neuropsychology	None	NA [UL (+/-) motor control with RCTs]
Intermittent compression	Tactile and proprioceptive	Neurophysiology	Yes (+)	NA [UL (+) motor control with RCTs]
CIMT	Visual and verbal	Neuropsychology	None	UL (+)
PBWSTT	Visual and proprioceptive	Neurophysiology/neuropsychology	None	LL (+) motor and gait function
Thermal stimulation	Hot and cold agent	Neurophysiology/neuropsychology	Yes (+)	NA [UL/LE (+) motor control with 5 RCTs]

[1]Obtained from meta-analyses or systematic reviews. CIMT: Constraint-induced movement therapy; PBWSTT: Partial body weight-supported treadmill training; +: Positive effect; -: No better than the control group; LL: Lower limb; UL: Upper limb; NA: Not available; RCT: Randomized clinical trial.

involved in tactile or mechanical stimulation, as shown in functional brain imaging studies of healthy subjects[75,76]. In RCTs, TS significantly improved several aspects of the upper- and lower-limb outcomes of acute and subacute stroke patients[74,77-80] when combined with standard rehabilitation therapy. Comparable enhancement was also observed and maintained in the lower-limb outcomes at the 3-mo follow-up but disappeared at the 6-mo follow-up[79]. The use of TS in rehabilitation not only provides sensory stimulation but also deploys the forced-use strategy to provoke volitional/reflexive motor activity. Neural plasticity may be a reason for the effect of TS in stroke patients. TS can be a low-cost, practicable intervention using home-made materials, such as a water pack. Thus, TS can easily be established as a generally popular home-care therapy. Table 2 summarizes the characteristics of the stimulation modalities used in recent rehabilitation programs.

A "TRAINING PACKAGE" CONCEPT FOR REAHBILITATION

Both conventional rehabilitation strategies and the recently developed advanced treatments mostly emphasized the motor functional outcomes and viewed various types of sensory stimulation (inputs) or feedback as crucial components in stroke rehabilitation[7,13-17,34-38,41-43,46,63,74]. A large number of robust large-scale studies of evidence-based treatments for stroke rehabilitation have been published in recent decades[7-11]. These studies provide evidence that advanced rehabilitation methods significantly enhance functional outcomes during particular phases of recovery from stroke. In addition to the significance of the advanced rehabilitation therapies, knowing the ideal and most powerful training strategies for recovery during the acute, subacute to chronic phases is very helpful to stroke patients and therapists. Before we describe the concept of an ideal training program (a training package), several perspectives need to be considered.

First, no clear evidence indicates that the recently developed rehabilitation therapy can replace any of the treatments based on physiotherapeutic "schools" that are generally viewed as the standard rehabilitation treatments for stroke. In general, most of the specific rehabilitation strategies have been adopted or added as supplementary methods by therapists to reinforce functional recovery after stroke. The significance of the advanced therapies, such as ES[37,38,42], robotic therapy[46], virtual reality therapy[62], PBWSTT[59,60], and CIMT[71,73], has been derived through meta-analysis of stroke patients in a particular phase. However, no large longitudinal study that integrated these advanced therapies to treat stroke patients throughout the entire rehabilitation process has been conducted.

Second, previous studies focused mostly on comparing the effect of specific treatments within a particular period following stroke, either in the acute/subacute or chronic phase. However, the progress of stroke recovery is dynamic and individualized, dependent on the nature of the injury, the patient's characteristics and other intrinsic or extrinsic factors[10,11]. Faced with the dynamic alteration of motor function, there is no evidence to support that any single intervention plays an important role in achieving the maximum benefit throughout an entire rehabilitation process, from acute to subacute to chronic status. Due to the diversity of the advanced treatments and the heterogeneous methodologies applied, previous meta-analyses or systematic review articles generally focused on the effect of a single specific treatment[9,14,36-38,42,46,60,62,71,73]. Thus, it is difficult to compare their performance in a time-related progression.

Third, very few studies have systematically evaluated the optimal intensity and/or duration of a specific intervention. Thus, it is unclear what the threshold of an effective "dose" of an intervention might be or how long an effective intervention should be applied. As a result, the intervention may cease before rehabilitation reaches a peak. Lastly, therapy in clinical practice is often provided for only a few weeks, generally 4 to 8 wk[9,14,31,36-38,42,46,60,62,73]. A therapy may fail to provide comprehensive progression in the intensity and task complexity because the optimal frequency and duration of treatment sessions are undetermined. Moreover, therapists often use the treatments either single or combined with other treatments in clinical practice according

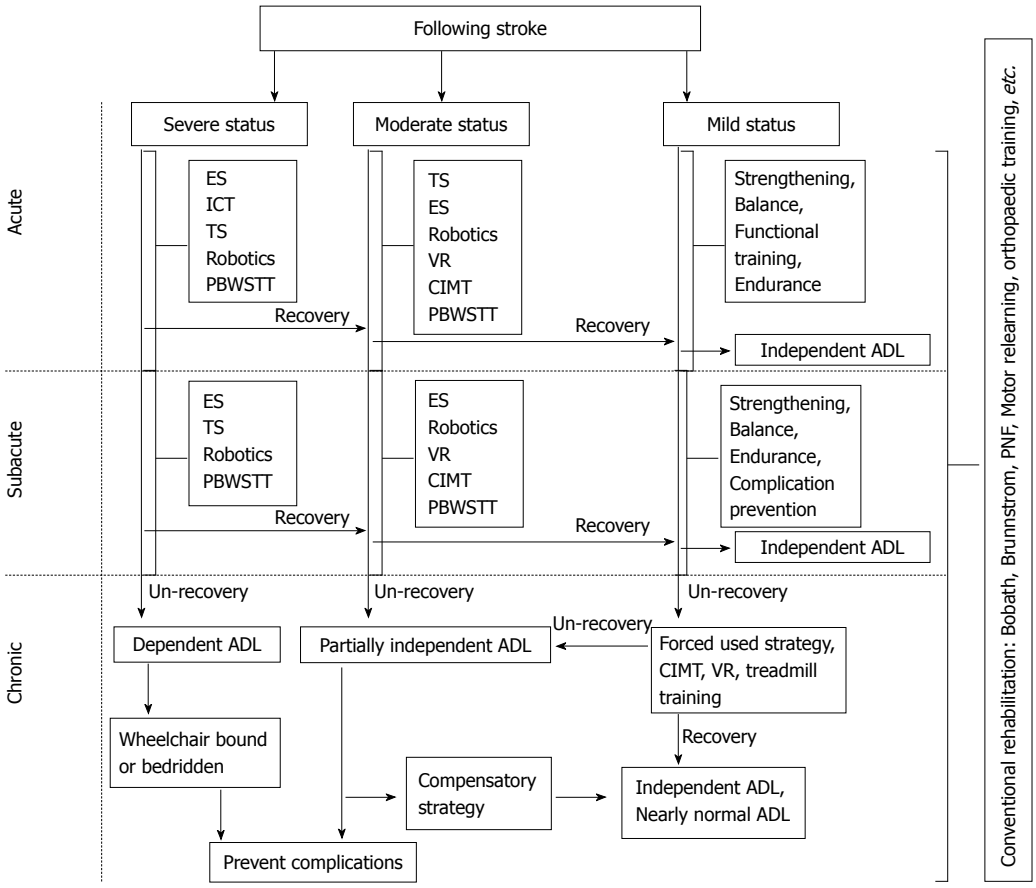

Figure 1 Schematic flowchart for selecting from the available rehabilitation strategies for stroke patients with impairments of various severity levels during different stroke phases. Functional recovery from a severe to moderate and mild condition after stroke is indicated by arrows with indications of the progression of recovery and unrecovery. Appropriate advanced rehabilitation technique(s) combined with conventional rehabilitation are selected to maximize the patient's functional recovery according to his/her initial motor function (mild, moderate or severe) in the clinic. ADLs: Activities of daily living; CIMT: Constraint induced movement therapy; ES: Electrical stimulation; PBWSTT: Partial body weight supported treadmill training; PNF: Proprioceptive neuromuscular facilitation; TS: Thermal stimulation.

to the patient's status and progress during the recovery phase. Therefore, customizing the available interventions during different recovery phases after stroke to meet the needs of the patient's current status to optimize the outcomes will be a major challenge for therapists.

A single or two rehabilitation approaches can be easily used in the clinic and home, and these strategies must be based on the individual's progression throughout the rehabilitation period. Combining valuable treatments is believed to be a good tactic for facilitating the restoration of functional mobility. It is generally believed that treatments could be given in a parallel or sequential way depending on the patient's recovery process and her/his functional status. Figure 1 shows a schematic diagram of the available techniques that are suggested for patients with different functional status during the three stroke phases. Based on the available evidence described above, the appropriate advanced intervention combined with a conventional rehabilitation treatment has been summarized for stroke patients with impairments of different severities. Functional progression is indicated by arrows in terms of the outcome, *i.e.*, recovery or unrecovery. The therapist can easily select the appropriate strategies to maximize the functional outcome of stroke patients.

For instance, if a patient shows little or no voluntary movement of the paretic limb (severe status) during the early poststroke stage, rehabilitation through task-oriented training is often difficult to apply[50-57]. Most of newly developed therapies, which require a minimal motor ability, cannot be utilized during the early phase of recovery of stroke patients[40,49-50,53-58]. ES[35-37], TS[74,78-79] and robotics-aided treatments[44,46,48] provide significant improvement in several aspects of motor or functional activities, particularly for those in the initial phase of recovery from moderate to severe strokes who show little or no voluntary movement. Thus, these techniques could be chosen to treat or activate motor activity in the paretic limbs. Until the patient' condition has progressed to a moderate or mild status, alternative interventions, such as VR, CIMT or PBWSTT, which combine strengthening and functional training strategies, can improve the outcome. From a practical perspective, the training package schematic shown in Figure 1 provides selective strategies for the initial phase of recovery to the subsequent recovery process for stroke patients with a different severity status. Although the various interventions are categorized according to the severity status, an optimal rehabilitation program (the ideal training package) can be individualized

and needs to be further investigated.

An appropriate protocol for a selected group of patients plays an important role in terms of cost-effectiveness, limiting the period of hospitalization and minimizing the labor of the therapist during the early phase of stroke recovery. For example, in terms of a "training package", when therapists need to decide the clinical plan for the upper limb rehabilitation of acute stroke patients with a moderate to severe status during the initial stage, the TS technique would be the choice that facilitates active movement cost-effectively as early as possible. When a certain degree of voluntary movement is elicited in the stroke patient, the therapist can apply other suitable techniques, such as CIMT or forced use with a task-oriented approach. Ideally, a protocol combining several rehabilitation strategies at the right time, as "a training package", could maximize the patient's progress during recovery. Although we propose a reasonable strategy for planning a rehabilitation roadmap based on the available evidence for a particular status of stroke, the ideal training package for the progression of a stroke patient remains to be determined.

CONCLUSION

Rehabilitation is a long process for a stroke patient. How to choose the appropriate route(s) in a complex roadmap for stroke patients whose status differs during the phases of their recovery is always a great challenge to the clinician, patient and family. Conventional rehabilitation therapies (including the Bobath, PNF, motor relearning and Brunnstrom techniques, either singly or combined) are the regular or routine treatments applied in stroke rehabilitation units. Several advanced rehabilitation strategies with a strong evidence basis have been developed and are summarized here. According to the patient's mobility status and recovery phase, the appropriate advanced rehabilitation therapy combined with conventional rehabilitation treatment comprise a training package. This training package may provide suggestion for therapists to maximize the improvement of stroke patients in the right timeframe. To further validate the usefulness of the training package approach, longitudinal or serial studies of the outcomes of selected and combined therapies are important.

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MINIREVIEWS

Dissociative symptoms and dissociative disorders comorbidity in obsessive compulsive disorder: Symptom screening, diagnostic tools and reflections on treatment

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Abstract

Borderline personality disorder, conversion disorder and obsessive compulsive disorder frequently have dissociative symptoms. The literature has demonstrated that the level of dissociation might be correlated with the severity of obsessive compulsive disorder (OCD) and that those not responding to treatment had high dissociative symptoms. The structured clinical interview for DSM-IV dissociative disorders, dissociation questionnaire, somatoform dissociation questionnaire and dissociative experiences scale can be used for screening dissociative symptoms and detecting dissociative disorders in patients with OCD. However, a history of neglect and abuse during childhood is linked to a risk factor in the pathogenesis of dissociative psychopathology in adults. The childhood trauma questionnaire-53 and childhood trauma questionnaire-40 can be used for this purpose. Clinicians should not fail to notice the hidden dissociative symptoms and childhood traumatic experiences in OCD cases with severe symptoms that are resistant to treatment. Symptom screening and diagnostic tools used for this purpose should be known. Knowing how to treat these pathologies in patients who are diagnosed with OCD can be crucial.

Key words: Dissociation; Obsessive compulsive disorder; Screening and diagnostic tools

Core tip: The literature has demonstrated that the level of dissociation might be correlated with the severity of obsessive compulsive disorder (OCD) and that those not responding to treatment had high dissociative symptoms. The structured clinical interview for DSM-IV dissociative disorders, dissociation questionnaire, somatoform dissociation questionnaire and dissociative experiences scale can be used for screening dissociative symptoms and detecting dissociative disorders in patients with OCD. However, a history of neglect and abuse during childhood is linked to a risk factor in the pathogenesis of dissociative psychopathology in adults. The childhood trauma questionnaire-53 and childhood trauma questionnaire-40 can be used for this purpose.

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INTRODUCTION

The term dissociation was used by James in 1890 from the translation of the French term *désagrégation* after it was described by Pierre Janet in 1889. Pierre Janet described dissociation as the deterioration in the unification of experiences at the mental level. These experiences consisted of perception, memory, cognition and emotions. Normally, these experiences all together constituted wholeness in the stream of mind[1,2]. Patients perceive dissociation as dispersion in the wholeness of sense of self. This

dispersion emerges as the deterioration in the unity of chronological, biographic and perceptive identity[2,3].

Dissociative disorders were first described as categorical independent nasographical cases in the Diagnostic and Statistical Manual of Mental Disorders (DMS-Ⅲ) which was published in 1980. Before that, they were among the phenomena associated with dissociative symptomatology hysteria[1,2].

According to DSM-IV-TR, dissociation is described as the deterioration in the integrative functions of consciousness, like the perception of memory, identity and environment. On the other hand, in the etiology of dissociation, traumatic experiences, especially like childhood abuse, take an important place[4,5]. Dissociation functions as the autohypnotic defense mechanism that provides the psychological wholeness of the individual against these traumas[6]. Dissociative disorders contain a group of clinical syndromes associated with the deterioration of one or more of these features described. Dissociation may have a sudden or gradual, temporary or chronic stream. Among the dissociative disorders, the type that has the most chronic and complex features and that contains all the other dissociative phenomena is the dissociative identity disorder. Other dissociative disorders are depersonalization disorder, dissociative amnesia and dissociative fugue disorder. On the other hand, the category that does not meet the specific diagnostic criteria is described as the dissociative disorder that cannot be named otherwise. According to some writers, in cases when the prevalence of dissociative disorders is used as a base for the DSM-Ⅳ diagnosis criteria in clinical practice, it cannot be estimated. These disorders may go unnoticed in clinical practice and it is thought that they are more widespread than estimated. Besides, there is no research based on large populations[2,3]. However, according to recent research, the frequency is estimated to be 5.6% to 10% in the general population[1]. Despite the fact that they are a separate diagnostic category on their own, dissociative symptoms can be observed together with almost all the psychiatric disorders. They can affect the clinical stream of the psychiatric disorders that they are found with[7]. Dissociative symptoms are frequently found with borderline personality disorder[8,9], conversion disorder[10] and obsessive compulsive disorder[11].

Obsessive compulsive disorder (OCD) is a disorder frequently encountered and its lifelong prevalence is between 1% and 3%[4]. OCD is an illness that generally has a chronic stream. This disorder is characterized by obsessions or compulsions, takes very much of the person's time and causes intense stress or affects the individual's personal life[12].

DISSOCIATIVE PROCESSES AMONG PATIENTS WITH OBSESSIVE COMPULSIVE DISORDER

OCD is phenotypically very heterogeneous. This disease has several manifestations, with various dimensions regarding symptoms. In this study, 50 patients who had been diagnosed with OCD were investigated in terms of dissociative symptoms and the relationship of these with symptom dimensions of OCD. In general, dissociative scores were correlated with the level of severity of OCD. However, the controlling dimension was the parameter that was most closely correlated with dissociation. Amnesic dissociative symptoms were found to be correlated with controlling compulsive scores[11].

Rufer *et al*[13] evaluated 52 patients with the diagnosis of OCD. In this study, Cognitive Behavioral Therapy (CBT) was administered to patients for 9.5 wk on average and patients received exposure therapy. In this study group, a high level of dissociative symptoms was detected in patients who ceased treatment because of non compliance. In 43 patients who continued the treatment, however, those with severe OCD symptoms and not responding to the treatment had high dissociative symptoms. In this study, it was reported that high dissociative symptoms can be an indicator for poor response to CBT.

In a study where Belli *et al*[14] included 78 OCD cases, a significant relationship between severity of obsessive compulsive symptoms and dissociative symptom levels was detected. Dissociative disorder dual diagnoses were also investigated using SCID-D. The rate of having at least one dissociative disorder in study group was 14%. In this study, the most common dissociative disorder was depersonalization disorder, followed by dissociative amnesia and dissociative identity disorder. These diagnoses indicated that complicated dissociative disorders accompanied OCD considerably. In another study, Belli *et al*[15] found high levels of dissociative symptoms and a significant correlation between these symptoms and obsessive compulsive symptoms was noted. However, no significant relationship between dissociative symptoms and childhood traumatic experiences was detected.

Semiz *et al*[16] divided the patients into two groups in a study which included 120 OCD patients. Fifty-eight of these patients constituted the treatment-resistant group, whereas the treatment-responding group included 62 patients. The groups were compared to each other. The treatment-resistant group had a higher level of disease severity, dissociative symptoms and childhood traumas. The results of this study suggested that dissociative symptoms and childhood traumatic experiences can precede poor response to treatment.

In another study, Selvi *et al*[17] investigated 95 OCD patients from a different aspect. In this study, the relationship between possible dissociation, childhood trauma and cognitive processes in patients with OCD was investigated. It was found that dissociative symptomatology was strongly related to pathological processes that constituted OCD symptoms.

One of the most important methods for the treatment of OCD is Cognitive Behavioral Therapy (CBT). Pathological cognitive processes are looked for in the

formulation of treatment in OCD. However, no adequate response to CBT was reported in 30%-60% of cases. This also requires consideration of multifactorial intrapsychic structures that constitute OCD. The hypnotherapeutic approach that focuses on dissociative phenomena is one of the most important of these factors. Hypnotherapeutic approaches can also be used in the treatment of OCD[18]. It was reported that dissociative symptomatology can be a very important factor in not responding to treatment. This condition can involve not only treatment resistance to CBT, but also cases who do not adequately respond to medication[19]. However, the relationship between dissociative symptomatology with childhood traumatic experiences was well established. Hypnotherapeutic approaches can also be used in repairing the traumatic memory[20]. It is apparent that systematic studies are needed to measure the efficiency of hypnotherapeutic approaches in treatment resistant cases in regards to relevant dissociative pathology. Ego state therapy, a systematic approach in which hypnotic phenomena are used[21], can be beneficial in the treatment of complex conditions, such as the dissociative amnesia or dissociative identity disorder that accompany OCD.

ASSESSMENT OF DISSOCIATION SYMPTOMS AND CHILDHOOD TRAUMATIC EXPERIENCES IN PATIENTS USING THE TOOLS AND SCALES

The structured clinical interview for DSM-IV dissociative disorders

SCID-D is a semi-structured interview tool developed by Steinberg. It is used to explore and determine the dissociative disorders according to DSM-IV. By using this interview tool, dissociative identity disorder, depersonalization disorder, dissociative amnesia, dissociative fugue and the dissociative disorder diagnoses that cannot be named otherwise can be established. Because of the fact that the dissociative identity disorder diagnosis can meet the symptoms of all the other diagnosis categories, it is generally established on its own. If this diagnosis is established, then generally no other diagnoses are established[22].

Dissociation questionnaire

This scale was developed by Svedin *et al*[23]. By using this scale, dissociative experiences are explored and the severity of these symptoms is evaluated. This scale can be used to explore the traumatic experiences of psychiatry patients and consists of 63 questions. Individuals mark the choices appropriate to them. Every heading is evaluated by a point between 1 and 5 and the average score is obtained by dividing the total points by 63[23].

The somatoform dissociation questionnaire

This scale is a self-rating instrument that consists of 20 articles that patients themselves fill out, used in the exploration of somatoform symptoms of patients who have had traumatic experiences. Every heading is evaluated by a point between 1 and 5 and the average score is obtained by dividing the total points by 20. This scale was developed by Nijenhuis *et al*[24].

The dissociative experiences scale

This scale is a psychological self-rating instrument that evaluates dissociative symptoms. The scale contains 28 questions, a general score and four sub scales. Every heading is evaluated by a point between 0 and 100 and the average score is obtained by dividing the total points by 28[25].

A history of neglect and abuse during childhood is linked to a risk factor in the pathogenesis of dissociative psychopathology in adults[5,26-29]. Dissociation is also linked to traumatic life events, especially childhood traumas[30]. Therefore, childhood traumas must be investigated when dissociative symptoms are found in patients with an OCD diagnosis. This could be very important in planning treatment and the following scales can be used for this purpose.

Childhood trauma questionnaire (CTQ-53)

This is a self-rating scale developed by Bernstein *et al*[31] consisting of 53 questions. With this scale, childhood emotional, physical and sexual abuse and childhood physical and emotional neglect situations are evaluated. Points between 1 and 5 are given for all types of possible childhood traumas and the total of the points are derived from the total points of every childhood trauma between 5 and 25. The measurement also contains the minimization/denial scale that has three headings and is potentially out of the rating[31]. The 3 items comprising the minimization/denial scale are dichotomized (never = 0, all other responses = 1) and summed; a total of one (1) or greater "suggests the possible underreporting of maltreatment" false negatives.

Childhood trauma questionnaire (CTQ-40)

This scale was developed by Bernstein *et al*[31]. It consists of 40 questions and every question has five choices. It is a self-rating scale that explores childhood traumatic experiences before the age of 18. The answers are composed of five choices. These answers are: never (1); rarely (2); sometimes (3); often (4); and very often (5). High scores reveal that abuse in adolescence and childhood took place very often. The total points are between 40 and 200[31].

CONCLUSION

OCD is a disorder with high lifelong prevalence that can severely deteriorate the quality of life. Therefore, every aspect influencing the development and treatment of this disorder should be addressed seriously.

The individuals diagnosed with OCD can be evaluated in three categories in an etiological context. These dimensions can be classified as cognitive, biological and

emotional[32,33]. Some writers emphasize the importance of traumatic dissociative, existential and acquired developmental factors in the etiology of OCD of some patients in the emotional dimension. For many years, various treatments have been suggested for the treatment of OCD. It is frequently emphasized that cognitive behavioral therapy is one of the most effective treatment methods[34]. Some authors[20,35,36] indicated that the therapist should target the stress eugenic factors that are acquired in intrapsychic and developmental ways and that contain conflicts, existential traumas and dissociated pieces of personality in order for the OCD symptoms to be treated successfully. However, the relationship between dissociative symptomatology and childhood traumas has not been clearly defined. To a large extent, dissociation is especially related to childhood abuse[26,37]. Dissociation functions as the autohypnotic defense mechanism that provides the psychological wholeness of the individual against these traumas[4,5]. In addition to the cognitive behavioral model, different methods can also be used in the treatment of dissociative symptoms and chronic dissociative disorders. Some writers stated that ego state therapy and hypnotherapy can be effective on dissociative processes. In the ego state therapy, hypnotic phenomena are used as the basic technique. In this therapy method, it is thought that the self develops in a fragmented way and functions by becoming integrated. Childhood trauma and stresses can disrupt this integrity. During the therapy, these childhood experiences are concentrated on again in order to fix the disrupted integrity. It is apparent that systematic studies are needed to measure efficiency of hypnotherapeutic approaches in treatment resistant cases in regard to relevant dissociative pathology. Ego state therapy is a systematic approach in which hypnotic phenomena are used[20,21].

Investigating the dissociative symptoms, complex dissociative disorders and childhood traumas is very important in patients who are diagnosed with OCD. Clinicians should not fail to notice the hidden dissociative symptoms and childhood traumatic experiences in OCD cases with severe symptoms and resistant to treatment. Symptom screening scales and diagnostic tools used for this purpose should be known. To know how to treat these pathologies in patients who are diagnosed with OCD, particularly in cases with resistance to treatment, can be crucial.

OCD is a disease with high lifelong prevalence that can severely deteriorate the quality of life. The literature has demonstrated that the level of dissociation might be correlated with the severity of OCD and that those not responding to treatment had high dissociative symptoms.

It is important to know the scales that explore the dissociative symptoms and childhood experiences for patients diagnosed with OCD. Apart from that, the tools that serve to diagnose complex and chronic dissociative disorders can also help. More research that investigates the relationship between OCD and dissociative processes are needed. These studies need to have a large sample size that comprises both genders. As these studies increase, serious developments will take place in treatment plans.

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Metabolic syndrome and childhood trauma: Also comorbidity and complication in mood disorder

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Abstract

Studies for prevalence and causal relationship established that addressing comorbidities of mental illnesses with medical disease will be another revolution in psychiatry. Increasing number of evidence shows that there is a bidirectional connection between mood disorders and some medical diseases. Glucocorticoid/insulin signal mechanisms and immunoenflammatory effector systems are junction points that show pathophysiology between bipolar disorder and general medical situations susceptible to stress. A subgroup of mood disorder patients are under risk of developing obesity and diabetes. Their habits and life styles, genetic predisposition and treatment options are parameters that define this subgroup. Medical disease in adults had a significant relationship to adverse life experiences in childhood. This illustrates that adverse experiences in childhood are related to adult disease by two basic etiologic mechanisms: (1) conventional risk factors that actually are compensatory behaviors, attempts at self-help through the use of agents and foods; and (2) the effects of chronic stress.

Key words: Obesity; Dyslipidemia; Hypertension; Diabetes; Childhood trauma; Mood disorder

Core tip: Psychiatric and medical diseases have a two-way relationship, and may have some effects on each other's clinical appearance and clinical course, treatment options and choices as they affect the possibility of keeping links to carry the etiologic causes. The lifespan of people with serious and chronic disorders, such as mood disorder, decrease by 30% because of untreated medical diseases.

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INTRODUCTION

Studies for prevalence and causal relationship established that addressing comorbidities of mental illnesses with medical disease will be another revolution in psychiatry[1]. There is a bidirectional relationship between psyche and soma, each influencing the other. Plausible biological explanations are appearing at an astonishing rate. Psychiatric comorbidity with many chronic physical disorders has remained neglected. Evidence base of prevalence and causal relationship of psychiatric comorbidities in these disorders has been highlighted and strategies to meet the challenge of comorbidity have been indicated.

In our study on 2000 outpatient population, prevalence of medical diseases in mental illnesses, temporal relationship between appearance of medical diseases and mental illnesses and, whether treatment of mental illness is suitable for medical condition were cross-sectionally analysed, the rate of calculated of third axis co-diagnosis were as follows; 56% for mood disorders (MD), 42.3% for anxiety disorders (AD), and 38.3% for schizophrenia (S)[2]. The rate of calculated of third axis co-diagnosis

were different between MD, AD and S as follows; hypertension 34.4%, diabetes 23.6%, thyroid disease 18.5%, coronary arteria disease 13% in MD, hypertension 42.4%, respiratory disease 30.7%, gastrointestinal disease 25%, autoimmune disease 7% in AD, hypertension 65.3%, diabetes 14%, respiratory disease 12%, gastrointestinal disease 8% in S. The time interval between the beginning of disease to from now was detected as follows 6.19 ± 7.55/7.12 ± 8.15, similar in mood disorders (r = 0.912). Coefficient of correlation (r) were 0.265 and 0.425 for AD and S respectively (3.21 ± 3.15/8.34 ± 5.71 and 13.82 ± 11.36/8.21 ± 8.55). Our results revealed that MD and medical disease appeared simultaneously. The pharmacologically treatment of MD, AD and, S insuitable to the Ⅲ. Axis diagnosis and, found as high valuable mean in.

In bipolar disorder (BD), metabolic syndrome is more prevalent than general population. A subgroup of bipolar patients have higher risk of developing metabolic syndrome. Their habits, life styles, genetic susceptibility and choices of treatment are variables determining this subgroup, childhood trauma may be another variable. Metabolic syndrome has been reported at the rate of 35%-40% in bipolar patients. Metabolic syndrome encompasses obesity, diabetes, hypertension and dyslipidemia as cardiovascular risk factors. Although they are not among diagnostic criteria of metabolic syndrome, proinflammatory and prothrombotic state are considered in the framework of metabolic syndrome[3]. In our study, ICAM and VCAM levels measured at first manic episode were found to be higher than those found in subsequent remission period and healthy individuals. As our study group included only patients at first manic episode, there was no chronic effect of psychotropics use on these results. According to these results, probable cardiovascular disease (CVD) risk, reflected by increased ICAM and VCAM levels, is already present at the onset of the disease in bipolar patients[4].

Exploring the biological pathways that could account for the observed link show that dysregulated inflammatory background could be a common factor underlying metabolic syndrome and MD. Comorbid medical illnesses in bipolar disorder might be viewed not only as the consequence of health behaviors and of psychotropic medications, but rather as an early manifestation of a multi-systemic disorder[5]. It is also necessary to look for subgroups of MD based on their rates of comorbid disorders.

Psychiatric and medical diseases have a two-way relationship, and may have some effects on each other's clinical appearance and clinical course, treatment options and choices as they affect the possibility of keeping links to carry the etiologic causes. The lifespan of people with serious and chronic disorders, such as mood disorder, decrease by 30% because of untreated medical diseases[6]. Obesity and diabetes are most common metabolic disease, related hypertension, dyslipidemia and cardiovascular disease.

OBESITY

Obesity is a leading cause of preventable death and the prevalence of overweight and obesity is increasing. A survey of 4.115 adult conducted in 1999 and 2000 as part of the National Health and Nutrition Examination Survey found that 64.5% of the population is overweight and 30.5% is obese[7]. A separate, smaller study of 50 bipolar patients, found an obesity rate that was only slightly higher (32%)[8]. In this study, most of the weight gain occurred during acute rather than maintenance treatment, and the increase in body mass index (BMI) was related to severity of depressive episode. Although several studies have found significant obesity in bipolar patients[9]. It is difficult to ascertain the degree to which the obesity is secondary to medications used to treat bipolar disorder or to the illness perse[10]. In our study rate of overweight was 62% and obesity 8% of the first episode manic patients[11]. Longitudinal studies of children and adolescents have found a positive association of major depressive disorder with adult BMI. This association persisted even after controlling for age, gender, substance abuse, socioeconomic level and medication exposure[12].

Atypical antipsychotic medications are associated specifically with central obesity, which occurs when the main deposits of body fat are localized around abdomen. Accumulating evidence suggests that central deposition of body fat is a risk factor independent of overall obesity for mortality due to cardiovascular disease and type Ⅱ diabetes[13]. In our study BMI was predictive variable of the diabetes in first episode mania[11]. Other medications used the treatment affective disorders, including lithium, valproate, and some antidepressants, have also associated with weight gain. Thus far, there has been less concern regarding the development of metabolic syndrome with this drugs than with the atypical antipsychotics.

Beyond weight gain caused medications, symptoms of depressive episode itself can lead to obesity. Depressed mood leads to lower levels of activity. Depressive episodes with atypical features such as hyperphagia, hypersomnia, leaden paralysis and carbohydrate craving are more liable to lead to weight gain. In the majority of bipolar patients, however, depressive symptoms are far more frequent than manic symptoms[14]. Depression is often accompanied by hypercortisolemia, which is also associated with central obesity. Even in the context of normal body weight, hypercortisolemia has been associated with excess visceral fat deposition as measured by computed tomography scan[15]. A national survey of 40.086 adults examined the relationship between body weight was associated with major depression and suicidal ideation and suicide attempts[16].

DIABETES

Because overweight and obesity are associated with diabetes, many risk factors that have been linked to weight gain apply also to the development of diabetes. The prevalence of reported diabetes mellitus was found to be approximately three times higher in a sample of 345 hospitalized bipolar patients than in the general population (3.4%)[17]. Patients in this sample also had a more severe

course of their mood disorders such as rapid cycling and chronic course[18]. In a recent work which takes its sampling from the society, the ratio of present diabetes diagnosis among bipolar diagnosed cases is found to be higher than healthy individuals (10.8%)[19].

A subgroup of bipolar disorder patients are under risk of developing diabetes[9]. Their habits and life styles, genetic predisposition and treatment options are parameters that define this sub-group[12]. Metabolic syndrome and glucose abnormalities are reported between 18% and 30% in bipolar cases[18]. Among these, 7% are diabetes, while 23 % are pre-diabetes abnormalities.

Besides, the level of HbA1c in nonmedicated bipolar cases was found to be higher than the healthy controls[20]. In another similar study, hyperglycemia was found to be 43.5% in bipolar patients evaluated at the beginning of acute episode treatment[21]. According to the same study, 4.3% of the patients are under antidiabetic treatment. In a study of cases that exhibit violent (homicidal) behavior conducted by Langevin *et al*[22], it was reported that diabetes prevalence was found higher in the sampling group, and more importantly, diabetes diagnosis was missed out in more than 25% of the cases[22]. In the same group it was stated that manic and psychotic findings were found often and especially among the younger cases, injury crime was not rare.

In our study, DM diagnosis was determined as 18% among first manic episode bipolar cases. When evaluated with glucose metabolism abnormalities, this ratio becomes 64%[11]. In late onset bipolar cases evaluating cases aged over 50, 42% of cases have manic episode diagnosis related to general medical condition. In general medical conditions, the ratio of diabetes is 50%[12].

Dysregulation of the hypothalamic-pituitary-adrenocortical axis occurs frequently in patients with mood disorders. Hypercortisolemia associated with depressive states can lead to insulin resistance. Elevated levels of cortisol can lead to decreased insulin receptor sensitivity through currently unknown mechanisms[14].

A more hypothetical link between bipolar disorder and diabetes relates to intracellular signal transduction involving the enzyme glycogen synthase kinase-3-beta (GSK-3β). Glycogen synthetase kinase (GSK3) is a serine/threonine kinase that is a responsible enzyme from the cyclic mechanisms of the cell, gene expression, oncogenesis and neuronal protection[23]. Hippocampal volume and BDNF level decrease in diabetes[7]. Animal studies show that in diabetes-related depression, neurogenesis is inhibited in dentate gyrus[24].

Alterations in GSK-3β functioning play role in insulin resistance. Insulin inhibits GSK-3β which result enhanced glucose transport into skeletal muscle. Insulin mediated inhibition of GSK-3β leads as well to increased glucose utilization and the production of glycogen[25]. GSK-3β is also one of targets for lithium action. Lithium significantly inhibits brain GSK-3β at concentrations relevant fort he treatment bipolar disorder. Disturbances in the GSK-3β signal transduction pathway associated with diabetes may affect the viability of neurons that play a role in mood stabilisation. Diminished insulin mediated inhibition of GSK-3β may have an effect opposite to that of lithium and may ultimately lead to an accentuation of psychiatric symptoms related to bipolar disorder. Besides, in a clinical study intranasal insulin was found to be more effective than placebo on cognitive distortion in unipolar and bipolar euthymic cases[26].

When patients with diabetes are being treated, lithium should be used with care. Patients with juvenil onset insulin dependent diabetes are susceptible to diabetic nephropathy, and the risk is increased by the presence of hypertension. On the other hand, there is evidence that when lithium is combined with an oral antidiabetics or insulin, it has an assisting hypoglycemic effect in diabetic patients[27]. Lithium increases the sensitivity of glucose transport and metabolism in skeletal muscle and adiposytes. This effects similar to the effects of exercise.

In our study, free T4 levels have been found higher in diabetic first episode manic patients than nondiabetic first episode manic patients[11]. Thyroid Releasing Hormone (TRH -which is an endogen like antidepressant neuropeptide-) decreases the expression of GSK3-β[28]. GSK3-β activity, which increases in the manic phase of bipolar disorder, may be causing the reactive increase of free T4 by suppressing TRH.

In diabetic bipolar cases, triglyceride and cholesterol levels and BMI are determined as higher[11]. Triglyceride level and BMI are predictors in third and fourth order in regression analysis. When diabetes is in question, these findings are not a surprise, such that diabetes development is together with lipid metabolism abnormalities[10]. Also in our study, there is a correlation between triglyceride levels with fasting blood glucose and blood glucose level at the first hour of oral glucose tolerance test[11]. There is a stronger correlation between BMI with fasting blood glucose and HbA1c. In a recent work, the prevalence of obesity among bipolar cases was reported as 39.1%[29]. In the same study, high BMI, chronic course, longer disease period, lower functionality scores are shown to be comorbid with prevalent anxiety disorder, hypertension, diabetes and other diseases frequently. Additionally, in cases that show remission with lithium, BMI was found lower. In bipolar cases evaluated by Kim *et al*[21] at the beginning of acute period treatment, the ratio of hyperglycemia was determined as 43.5%. In the same study, 4.3% of the cases are under antidiabetic treatment, while 1.1 % of the cases are under anticholesterolemic treatment. There is hypercholesterolemia in 20.7% of the cases and obesity in 30.4% of the cases. All these findings should be considered as to question if the bipolar disorder itself acts like metabolic syndrome.

Increasing number of evidence shows that there is a bidirectional connection between mood disorders and some medical diseases[30]. Glucocorticoid/insulin signal mechanisms and immunoinflammatory effector systems are junction points that show pathophysiology between bipolar disorder and general medical situations

susceptible to stress[7]. In BD, the changes in brain energy metabolism and brain glucose metabolism may be important in BD pathophysiology[31]. Noradrenalin (NA), a signal molecule in the central nervous system, which has etiologic importance for many diseases is an important neurotransmitter in BD etiology[32]. High noradrenergic tonus, which is determined mostly genetically, may develop susceptibility for more than one medical and mental diseases in a wide spectrum for many people. So that, hypertension, progressive weight gaining, diabetes and mania are all conditions in which noradrenergic tonus increases. Since 1987, the prevalence of hypertension has been reported to be elevated (14%) in bipolar patients, compared to normal population (5.6%) and to unipolar depression (5%)[5]. This was replicated in several studies in USA and in Europe. While the largest study involving 25339 bipolar patients and 113698 controls found an increased rate of new-onset cases of hypertension among bipolar patients compared to general population and to schizophrenic cases.

Impaired fatty acid and phospholipid metabolism may be a primary cause of depression in many patients and may explain the interactions with other diseases. Postmortem analysis of brains of bipolar patients revealed that in orbitofrontal cortex of those subjects reduced DHC levels were detected due to elevated saturated fatty acids and arachydonic acid metabolism[31]. In manic patients both DHA and arachydonic acids levels were increased[33]. The same fatty acids and phospholipid mediated disruption of secondary messaging systems in BD is also operative in diabetes and vascular disease[34].

Hepatic steatosis, is more frequent among people with diabetes and obesity, and is almost universally present amongst morbidly obese diabetic patients. the links between hypercortisolism and obesity/metabolic syndrome, they hypothesize that this low prevalence of fat accumulation in the liver of patients with Cushing' s syndrome could result from the inhibition of the so-called low-grade chronic-inflammation, mainly mediated by interleukin 6, due to an excess of cortisol, a hormone characterized by an anti-inflammatory effect[35]. Moreover, insulin resistance is associated with lower serotonin levels. Visceral obesity, strictly linked to hepatic steatosis is specifically associated with mild to severe somatic affective-depressive symptom clusters. Previous data support the view that depression involves serotonergic systems, reflecting low levels of urinary 5- hydroxy-3-indoleacetic acid (5-HIAA). In Tarantino *et al*'s study[36], among metabolic indices, cholesterol, HDL-cholesterol, triglycerides and uric acid were not able to predict urinary concentrations of 5-HIAA, which were not associated with hepatic steatosis; vice versa, ferritin levels, and mainly HOMA values, were independent predictors of the urinary excretion of 5-HIAA. Dystimia/depression severity was negatively predicted by urinary 5-HIAA levels in the sense that the highest BDI values were forecast by the lowest values of urinary 5-HIAA. The importance of measuring the 24-h urinary excretion of 5-HIAA in follow-ups could rely on a method simultaneously mirroring the well-being status, the adherence to physical activity, which leads to improved insulin sensitivity, and the eating habits acquired by dystimic/depressed overweight/obese patients. In contrast, the significance of the urinary 5-HIAA is reduced in evaluating the severity of hepatic steatosis, likely because it is a structured process.

Recently, an increasing number of susceptibility variants have been identified for complex diseases. Somatic gene conversion and deletion were shown for BD, coronary arterial disease, rheumatoid arthritis, Chron's disease, hypertension and diabetes[37]. In a study of Lehne *et al*[38], comorbidity is mentioned between BD, Chron's disease and diabetes. At the same time, the concern of "missing heritability" has also emerged. There is however no unified way to assess the heritability explained by individual genetic variants for binary outcomes. A systemic and quantitative assessment of the degree of "missing heritability" for complex diseases is lacking. The diseases under evaluation included Alzheimer's disease, bipolar disorder, breast cancer, coronary artery disease, Crohn's disease, prostate cancer, schizophrenia, systemic lupus erythematosus (SLE), type 1 diabetes and type 2 diabetes[39]. The median total variance explained across the 10 diseases was 9.81%, while the median variance explained per associated SNP was around 0.25%. These results evaluated according to environmental impact assessment. This is because methylations and demethylations of DNA continue in primordial germ cells during of development within the terms of epigenetic principles. In fact, a substantial proportion of heritability remains unexplained for the diseases.

CONCLUSION

Medical disease in adults had a significant relationship to adverse life experiences in childhood (ACE). Examples of the links between childhood experience and adult biomedical disease are the relationship of ACE score to obesity, diabetes, coronary artery disease chronic obstructive pulmonary disease and autoimmune disease[40]. This illustrates that adverse experiences in childhood are related to adult disease by two basic etiologic mechanisms: (1) conventional risk factors that actually are compensatory behaviors, attempts at self-help through the use of agents and foods; (2) the effects of chronic stress as mediated through the mechanisms of chronic hypercortisolemia, proinflammatory cytokines and other stress responses on the developing brain and body systems, dysregulation of the stress response and pathophysiological mechanisms yet to be discovered. There is some biological correlates for adverse life experiences of childhood in bipolar patients. Early menarche and EEG abnormalities are some of them[41-43].

Individuals reporting a history of any childhood adversity had higher systolic and diastolic blood pressure[44]. Among subjects with a history of sexual abuse, a significant proportion met criteria for obesity, a trend

toward overweight was found for subjects with a history of physical abuse, although this relationship did not remain significant after adjusting for potential confounders. There was no statistically significant difference in the overall rate of dyslipidemia and/or metabolic syndrome between subjects with and without childhood adversity. The results herein provide preliminary evidence suggesting that childhood adversity is associated with metabolic syndrome components in individuals with mood disorders. An association between stressful events and episode recurrences has repeatedly been found in bipolar patients[45].

Psychological stress also may activate inflammatory responses in the brain[46]. The theoretical model frames the depressive episode as being a repair response to stress induced neuronal microdamage that can grade into a chronic neuroinflammatory condition. Cardiovascular damage and atherogenic changes could be a by-product of this process. One of the mechanisms whereby psychosocial stress influences both peripheral and central inflammatory cascade, is coordinated by autonomic nervous system. Thus, the release of noradrenaline and adrenaline follows the activation of the sympathetic system and induces the activation of both alpha and beta adrenoreceptors on immune cells thereby initiating the release of pro-inflammatory cytokines *via* the nuclear factor-kappa-beta cascade[47]. The brain is now known to be directly influenced by peripherally derived cytokines and gluco-corticoids as well as immune cells, which can access the brain through leaky blood-brain barrier and/or by activation of endothelial cells that line the cerebral vasculature, or bind to cytokine receptors[48].

A public health paradox is implicit in these observations. One sees that certain common public health problems, while being often also unconscious attempted solutions to major life problems, harken back to the developmental years. The idea of the problem being a solution, while understandably disturbing to many, is certainly in keeping with the fact that opposing forces routinely coexist in biological systems. Clinical evidence suggests that metabolism and emotion homeostasis might share common mechanisms.

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MINIREVIEWS

Pseudocyesis, delusional pregnancy, and psychosis: The birth of a delusion

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Abstract

Both pseudocyesis and delusional pregnancy are said to be rare syndromes, but are reported frequently in developing countries. A distinction has been made between the two syndromes, but the line of demarcation is blurred. The aim of this paper is to review recent cases of pseudocyesis/delusional pregnancy in order to learn more about biopsychosocial antecedents. The recent world literature (2000-2014) on this subject (women only) was reviewed, making no distinction between pseudocyesis and delusional pregnancy. Eighty case histories were found, most of them originating in developing countries. Fifty patients had been given a diagnosis of psychosis, although criteria for making the diagnosis were not always clear. The psychological antecedents included ambivalence about pregnancy, relationship issues, and loss. Very frequently, pseudocyesis/delusional pregnancy occurred when a married couple was infertile and living in a pronatalist society. The infertility was attributed to the woman, which resulted in her experiencing substantial distress and discrimination. When antipsychotic medication was used to treat psychotic symptoms in these women, it led to high prolactin levels and apparent manifestations of pregnancy, such as amenorrhea and galactorrhea, thus reinforcing a false conviction of pregnancy. Developing the erroneous belief that one is pregnant is an understandable process, making the delusion of pregnancy a useful template against which to study the evolution of other, less explicable delusions.

Key words: Pseudocyesis; Delusional pregnancy; Infertility; Prolactin; Delusion

Core tip: It is usually impossible to distinguish between pseudocyesis and delusional pregnancy. Both occur primarily in developing countries, and especially where there is strong familial and cultural pressure on women to be fertile. The delusion starts in a climate of apprehension and develops when sensory perceptions are interpreted as signifying pregnancy, despite evidence to the contrary. Understanding this delusion can help to understand other, more unusual false beliefs.

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INTRODUCTION

It is not uncommon for women to believe that they are pregnant when they are not. In jest this has been called "jestation". But it ceases being a jest when the preoccupation with pregnancy becomes an over-valued idea or a delusion. In women suffering from psychosis, delusional pregnancy is not uncommon, especially since the advent of antipsychotic medications, which, by virtue of inhibiting dopamine secretion, raise prolactin levels to produce amenorrhea, breast swelling/tenderness, and ga-

lactorrhea-akin to the somatic experience of pregnancy[1]. Moreover, antipsychotic drugs are associated with considerable weight gain, distending the abdomen and adding to a misperception of pregnancy. Even when there has been no prior sexual activity, fantasy-prone women can find ways of convincing themselves that they are pregnant. They imagine the implantation occurring by magic or through the wizardry of advanced reproductive technology. Such was the case of a 17-year-old girl reported by Manoj[2], who believed she was carrying a "test tube baby". Cruzado describes a further case where the imagined pregnancy was a product of "artificial insemination" and two more cases where impregnation was believed to have occurred *via* telepathy[3].

Another example was a patient (now deceased) who attended the Women's Clinic for Psychosis in Toronto, Canada[4].

CASE ILLUSTRATION

AC, a single 60-year-old woman, suffered from schizophrenia since age 16. After several inpatient admissions, she was being treated with depot antipsychotic medication, and was living independently, never completely free, however, of auditory, olfactory, and somatic hallucinations, nor of delusional thinking. At different times in her life AC developed romantic fantasies about men she met, her latest fantasy involving her psychiatrist, Dr. J. She knew Dr. J. was a married man but allusions to him on TV convinced her that he reciprocated her interest. After she watched a wedding on TV, she was persuaded that she and Dr. J. were secretly married. She began wearing a wedding ring and to believe that she was pregnant.

When asked how she could be pregnant since she had never had sexual relations, she stated that the depot injection she received monthly (prescribed by Dr. J.) had successfully implanted Dr. J.'s seed in her body and that she would soon be giving birth to his child.

A distinction has been drawn between pseudocyesis, where signs of pregnancy are demonstrably present (abdominal swelling, menstrual disturbance, spotting, the report of quickening, breast tenderness and engorgement, weight gain, galactorrhea) and delusions of pregnancy, where there may be cessation of menstrual periods and abdominal distension, but no other outward signs[5]. The first is said to be a somatoform disorder while the second is a symptom of psychosis[6]. More recently, however, with the growing recognition that elevated prolactin levels can lead to many of the signs of pregnancy, the two conditions (pseudocyesis and delusional pregnancy) are conceptualized as occurring on a continuum, sometimes in women with no prior or subsequent psychiatric history, sometimes in the midst of a depressive or related illness, sometimes in women suffering from ongoing psychotic illness[3,7]. What has been written about pseudocyesis applies equally well to the psychodynamics of delusional pregnancy. It may also apply to a range of related delusions centering around procreation[8,9], from the conviction of having an intimate partner (when none in fact exists), of being pregnant (when one is demonstrably not), of not being pregnant when one indeed is[10], of wrongly insisting, when in pain for other reasons, that one is undergoing labor and delivery[11], to the false idea of being a parent, a potentially dangerous delusion that has been known to lead to the kidnapping of other people's children[12].

In an effort to better understand the birth of delusions in general, the aim of this review is to focus on psychological, biological, and sociocultural antecedents as described in modern case reports of pseudocyesis.

The pertinent literature (Google Scholar, Pub Med databases) after the year 2000 was searched with the following terms: pseudocyesis, delusion of pregnancy, false/imaginary/phantom/pseudo/spurious pregnancy. All languages were included. Delusional pregnancy occurring in men or in species other than human was excluded. All the papers consisted of case reports except two[7,13], which used case control study designs.

EPIDEMIOLOGY

The case of AC described above from the Women with Psychosis Clinic is the 80th instance of delusional pregnancy/pseudocyesis reported since 2000, the 50th in whom the delusion emerged in the context of a prior psychotic illness. Although diagnosis is not always clear in the published reports, this suggests that, in most cases described in recent years, the affected women suffer from a concomitant psychotic illness. In the past, pseudocyesis has been reported as rare but, in developing countries, India[14] or sub-Saharan Africa[15], it is considered fairly common. It has a reported occurrence rate in Africa of 1 in every 344 pregnancies[16]. Over a period of 5 years, of 486 women with abdominal distension in Ghana who came for sonography thinking they might be pregnant, three were diagnosed with pseudocyesis (of the others, almost half had fibroids, 10% had a benign ovarian tumor, 10% had cancer of the cervix with ascites; about 7% suffered only from obesity)[17]. In Nigeria[18], five out of 242 women who came for sonography for gynecological complaints referable to the lower abdomen were diagnosed with pseudocyesis. Out of 3200 women presenting for infertility treatment in a teaching hospital in Sudan over a five-year period, 20 were diagnosed with pseudocyesis[19].

Though once said to occur only 1-6 times per 22000 births in the West[20], Moselhy *et al*[21] reported in 2000 that they ascertained three cases in a six month period on an acute psychiatric ward in Birmingham, United Kingdom.

The majority of cases of pseudocyesis are described in reproductive age women and 80% of the affected women are said to be married.

PHENOMENOLOGY

Delusional pregnancy can present as a monothematic de-

lusion[22,23] or, more commonly, in association with other delusions (polythematic delusions). Delusional pregnancy has presented in conjunction with Clerambeault's syndrome, as in the case of AC, or with Capgras syndrome[24]. It can present as a form of couvade syndrome, a "copy cat pregnancy" when a loved (and/or envied) intimate becomes pregnant[25-27]. It can be transient or long lasting, corrigible (or not) by demonstrated evidence, education, cognitive behavioral therapy, or psychopharmaceutical agents. It can be primary or appear in the context of medical conditions that cause abdominal distension such as fibroids[28], urinary retention[29], polydipsia[30], metabolic syndrome[31], tubal cyst[32] or abdominal pain such as cholecystitis[11]. Sonographs have picked up a number of additional potential causes of abdominal distension that can accompany pseudocyesis[33], such as abdominal neoplasm or enlarged liver. Neurological conditions can be associated with this delusion as, for instance, frontotemporal lobar degeneration[34,35]. Endocrine disturbance such as hypothyroidism can present as pseudocyesis[27]. It has been associated with the postpartum state[36], with premature menopause[37] and with high progesterone levels[38]. Most especially, pseudocyesis has been tied to hyperprolactinemia because elevated prolactin levels lead to many of the symptoms of pregnancy[1]. Hyperprolactinemia can result from psychological stress, especially the stress that accompanies a psychotic episode, independent of antipsychotic medication[39]. Prolactin levels can be raised by many organic conditions and by nipple stimulation as well as by drugs such as estrogens, antidepressants, antihypertensives, protease inhibitors, opiates, benzodiazepines, cimetidine, and dopamine blockers[40].

Antipsychotic drugs are all dopamine blockers and all raise prolactin level to some degree, some more than others, in a dose dependent fashion[41]. This means that women suffering from psychosis who are being treated with these agents often perceive body changes that they may associate with pregnancy[1]. This has been reported in several of the cases published since 2000[42-47]. Ahuja and Moorehead[13] describe six cases of pseudocyesis. Four of the six had been pregnant before and likened their current experience of high prolactin levels to the feeling they had during past pregnancies. In all six of these patients, the ideas/delusions of pregnancy disappeared soon after a change to a relatively prolactin-sparing antipsychotic.

Patient attributions-reasons given when confronted with the fact that blood tests and sonography were negative despite their own certainty that they were pregnant-vary according to cultural tradition and degree of patient education or sophistication. Absence of a fetus on sonography was explained by one patient by the probability that the fetus had migrated from her uterus to her back where he/she was hidden from view by bone and muscle[32]. A patient described by El Ouazzani[30] who had had six separate episodes of delusional pregnancy explained the pregnancies and the failure to confirm on possession by the devil. One of Dalfallah's patients[19], one of three wives in a polygamous marriage, attributed both her original infertility and her current "invisible" pregnancy to the envy of her husband's other wives and the witchcraft they exerted. Ruzanna and Marhani's patient[48] explained the apparent "loss" of her pregnancy by calling upon the Malay tradition of orang bunian, evil spirits taking possession of developing fetuses.

PSYCHOLOGICAL ANTECEDENTS

According to both Koic[49] and Ibekwe[15], pseudopregnancy always occurs in the context of a simultaneous wish and fear of pregnancy, *e.g.*, emotional conflict, stress, and ambivalence. It should be noted, as an aside, that anticipation and fear will substantially raise prolactin levels in many women, thus mimicking signs of pregnancy[50]. When there is pressure to conceive and simultaneous fear of pregnancy, the ground is laid for this form of delusion. Ambivalence may arise when a pregnancy, though unwanted, is seen as a possible means of recapturing a wayward lover, as illustrated in the case of the 15-year-old girl reported by Skrabic[51]. For women who live in societies where womanhood is defined by motherhood, as described in Dafallah[19], pregnancy, however problematic the circumstances, may still be wished for. In societies where women are rated by the number of their sons[14], a woman with only daughters will zealously pursue pregnancy, but ambivalently, fearing the birth of another girl. Simon[36] describe pseudocyesis among the Roma in rural Hungary where there is strong social pressure to become pregnant as soon as possible after marriage. At the same time, there is a high rate of maternal death during labor and delivery, making women ambivalent about pregnancy.

It was impossible to ascertain, in most of the case histories, whether the women described were infertile. Infertility, whether due to lack of a partner, menopause, gynecologic problems, prior sterilization, or concomitant illness, heightens the wish for pregnancy, while its very impossibility can fuel magical fantasies[15]. The timing of emergence of the delusion often coincides with the early stages of menopause[5,30,49,52,53], inferring that infertility plays a triggering role. Sometimes the timing suggests that the delusional pregnancy serves to compensate not only for the loss of fertility, but for loss in general. In the report by Marusic, the patient came to hospital a year after the death of her father, delusionally convinced that she was about to deliver a baby[46]. In Grover[44] a 46-year-old woman developed a psychosis two months after the death of an only son. The psychosis was treated with antipsychotic drugs, resulting in hyperprolactinemia and weight gain. Still on her medication, on the first anniversary of her son's death, the patient became convinced (falsely) that she was pregnant, that she felt fetal movements, and that the new baby was a male.

Some authors have suggested other related antecedents to the delusion of pregnancy such as social isolation, so that a baby becomes a hoped-for companion[54]. Ibekwe[15] has suggested that women's perception of their inherent powerlessness in a patriarchal society leads to

the development of pseudocyesis. Women in many developing countries, cannot compensate for lack of children, as can women in the West, by succeeding in a career, or making money in business or going out to war. Being pregnant (and gaining status thereby) is their one source of power.

In fact, because pregnancy is a highly respected state and women are treated especially well during this time by their spouses, in-laws, and society in general, giving up the pregnant state may be psychologically difficult. Simon *et al*[36] describe two cases where a delusional pregnancy occurred shortly after delivery, during the postpartum period, and seemed to be motivated by the wish to continue to be treated as if pregnant. Pregnancy confers advantages. In Muslim cultures, a husband cannot divorce his wife while she is pregnant[55]. In some religious traditions, pregnancy and breast-feeding absolve women from unwanted sexual activity[56].

From the results of their series of cases, Rosch *et al*[7] conclude that false pregnancy can be an unconscious adaptive strategy to guard against loss of a relationship. This view is seconded by Ibekwe[15] whose case describes an imagined pregnancy that brought the patient personal fulfillment, stability to her marriage and newfound acceptance from her in-laws. Ibekwe suggests that the delusion solved the dilemma faced by this infertile woman in a culture (Nigeria) that places immense value on children not only because procreation is religiously mandated, but also because it is economically necessary for survival and generational continuity. In sub-Saharan Africa, infertility is said to affect one third of all couples[57], is always blamed on the woman, and leads to discrimination and abuse[58]. In developing countries, violence against infertile women is reported to occur in 10 to 60 percent of instances[59,60].

EFFECTS OF CULTURE

Although perceived infertility is not always at the heart of delusional pregnancy[61], it contributes, more so in some social contexts than in others[62]. Infertility can cause extreme levels of distress[63,64], especially in developing countries where childlessness is never an acceptable option for married women, and where infertility treatments are often not available. Even where they are financially available, Islamic law forbids sperm and ova donations, as well as surrogacy[65]. Adoptions are also forbidden in most interpretations of Islamic law[66] because preservation of hereditary lineage is important. Infertility, though often caused by the male partner, is attributed, almost always in developing countries, to the woman[61]. A childless woman is viewed as a failure and is rejected by her husband and his family, as described in ethnographic studies carried out in the countries where pseudocyesis appears to be relatively commonplace[67-70].

Pronatalism, the belief that a woman's social value is linked to her production of children is strong in developing countries[71]. Only the presence of children gives a woman the right to share in her husband's property in sub-Saharan Africa. Infertility can be just cause for divorce or, in polygamous societies, justification for the husband taking another, more fertile wife[55,61]. The paradox is that infertility is relatively common in these same countries because of the prevalence of genital infection spread by unprotected sexual contact and because of unsanitary obstetric practices. To make matters worse, infant mortality is also high in many of these regions, partly because of the popularity of consanguineous marriages[72]. This translates into pressure on couples to give birth to as many children as possible, to insure against loss. In some traditional societies, the pressure to produce children is experienced as coming not only from family members but also, importantly, from dead ancestors who may feel wronged by the lack of descendants, and take revenge[73].

The role of cultural factors is evident in the identifications that women sometimes make when they develop a delusional pregnancy. The best illustration of this is in Battacharyya and Chaturvedi[6] who describe a woman from Bangalore India who believed that, in a previous birth, she had been the wife of the Hindu god Lord Rama and was now pregnant by him. In Hindu legend, Rama and his wife Sita are the personifications of ideal love, but are destined to be separated from each other. Furthermore, Sita (like the woman in question) gives birth to her twin sons when she is alone.

Where it is commonplace to believe that magic and evil spirits can cause disease, the distinction between a belief and a delusion can be easily blurred, as in Saudi Arabia, for instance, where many believe that pregnancy does not require sexual contact, but can be induced by spirits[55].

BIRTH OF A DELUSION

The delusion of pregnancy, as exemplified by the 80 cases reported since 2000, illustrates the circumstances of birth and development of a delusion. According to Conrad[74], the first stage, which he called "das trema" is a general feeling of non-specific apprehension. This can be a result of familial and societal pressures or personal aspirations to become pregnant despite obstacles such as infertility, old age, spinsterhood, ill health, poor marital relationship, or inadequate socioeconomic conditions. The general apprehension during this first stage may follow the loss of a child, or loss of status, or loss of a love relationship. The second stage of delusion formation is a sensory perception, such as weight gain, or vaginal spotting, or abdominal movement, or frequency of urination. The same sensory perception may have occurred many times before but, this time around, as the person searches for what it might mean, it suddenly acquires extraordinary significance. This is the third stage, where meaning is attached to an otherwise neutral sensation. The meaning, seemingly of surreal importance so urgent is its message, appears "out of the blue" ("Ah, I must be pregnant!")[75]. It feels convincingly true because, in one fell swoop, it resolves the difficult dilemmas with which the woman has

been struggling ("How can I live without my son?" "How can I be a woman if I'm infertile?" "How can I hold on to a man who is no longer interested?" "How can I avoid sex and still be a wife?")[76]. How a person then deals with this momentous information depends on personal factors (health, education, reasoning ability, cognitive biases) and on situational factors (family, socioeconomics, culture, religion). Such factors may serve to dispel the delusion for want of evidence and plausibility or they may serve to reinforce it by recalling traditional beliefs and fictional accounts[77].

FUTURE DIRECTIONS

A better understanding of pseudocyesis/delusional pregnancy requires experimental study designs. Antecedents, onsets, and diagnoses could be compared in (1) women and men with this condition[78]; (2) fertile[61] and infertile women; and (3) pseudocyesis and other monothematic delusions such as Capgras syndrome or Cotard syndrome[79]. It may also prove interesting to compare, on the same variables, women who delusionally deny pregnancy[10] with those who delusionally insist, against all evidence, that they are pregnant. Such careful comparisons will shed more light on this and other delusional conditions.

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RETROSPECTIVE STUDY

Tree stand falls: A persistent cause of neurological injury in hunting

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Abstract

AIM: To characterize and compare our current series of patients to prior reports in order to identify any changes in the incidence of neurological injury related to hunting accidents in Rochester, New York.

METHODS: All tree stand-related injuries referred to our regional trauma center from September 2003 through November 2011 were reviewed. Information was obtained from the hospital's trauma registry and medical records were retrospectively reviewed for data pertaining to the injuries.

RESULTS: Fifty-four patients were identified. Ninety-six percent of patients were male with a mean age of 47.9 years (range 15-69). The mean Injury Severity Score was 12.53 ± 1.17 (range 2-34). The average height of fall was 18.2 feet (range 4-40 feet). All patients fell to the ground with the exception of one who landed on rocks, and many hit the tree or branches on the way down. A reason for the fall was documented in only 13 patients, and included tree stand construction (3), loss of balance (3), falling asleep (3), structural failure (2), safety harness breakage (3) or lightheadedness (1). The most common injuries were spinal fractures (54%), most commonly in the cervical spine (69%), followed by the thoracic (38%) and lumbar (21%) spine. Eight patients required operative repair. Head injuries occurred in 22%. Other systemic injuries include rib/clavicular fractures (47%), pelvic fractures (11%), solid organ injury (23%), and pneumothorax or hemothorax (19%). No patient deaths were reported. The average hospital length of stay was 6.56 ± 1.07 d. Most patients were discharged home without (72%) or with (11%) services and 17% required rehabilitation.

CONCLUSION: Falls from hunting tree stands are still common, with a high rate of neurological injury. Compared to a decade ago we have made no progress in preventing these neurological injuries, despite an increase in safety advances. Neurosurgeons must continue to advocate for increased safety awareness and participate in leadership roles to improve outcomes for hunters.

Key words: Neurological sports medicine; Hunting; Tree stand falls; Spine injury; Traumatic brain injury

Core tip: Hunting is a popular sport and hunters have devised numerous ways to increase their advantage against their quarry. Tree stands have been developed to allow hunters better sight and increased protection. However, improper use, faulty construction, and other factors can increase the risk of injury, specifically to the

central nervous system. We present the data obtained at our institution over an eight-year period cataloging the injuries obtained while using tree stands. We have begun outreach to the community with our findings, with the goal of increasing awareness and education to reduce risks and increase hunter safety.

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INTRODUCTION

Hunting is a popular sport and recreational activity nationwide, with nearly 15 million licensed hunters in the United States and approximately 680000 in New York State according to the Fish and Wildlife Service[1]. Hunting is a favorite pastime for those in the Rochester, NY area that spans all age ranges. Hunters age 12 and above may obtain a hunting license in New York and most use bows or firearms to hunt a variety of wildlife animals. Over time, hunters have developed various methods to improve the leisure of the sport. One such method is the elevated tree stand.

Tree stands, also referred to as deer stands, are elevated platforms or seats that can be built in, nailed, locked, or rested up against a tree. Stands give hunters an advantage of wider visibility, while decreasing the chances of being detected by sight or scent[2-4]. Hunting tree stands can be commercial or homemade, and are usually installed 15 to 30 feet above ground. Commercial tree stands typically have a two-by-two feet platform seat, and may or may not be attached to the tree by safety belts, a harness, or straps. These safety straps are designed to help prevent the hunter from falling from the tree or stand.

Hunting related accidents and injuries have been largely attributed to falls from tree stands[2]. This is the most common way hunters are injured, debunking the popular misconception of intoxicated hunters sustaining self-inflected ballistic injuries[5]. Estimates reveal that nearly 10% of hunters who use tree stands are injured annually, and more than 75% of tree stand injuries occur while using fixed position or climbing stands[6]. As much as 75% of the time spent during a hunt is spent on tree stands, and tree stands are considered an essential component of large game hunting[6]. In North America, nearly 85% of hunters pursue large game (*e.g.*, deer, elk, bear, turkey, *etc.*), suggesting that the overwhelming majority of hunters have or will at some point use a tree stand[6]. When hunters fall from tree stands, they can reach a velocity of up to 30 mph. Yet these common hunting-related accidents often go unreported as victims only present to hospitals with serious injuries[3,4,7].

Falls from tree stands can lead to high impact injuries. One study demonstrated that 80% of fall victims required operative interventions, and nearly 10% of falls resulted in permanent neurological deficits or death[5]. The series of common injuries were fractures to the spinal cord, lower extremities, and traumatic brain injuries. The high morbidity of falls from tree stands have led to a small series of interventions to prevent devastating spinal cord injury through promoting the use of safety harnesses publicly[8]. It appears these interventions were successful as the incidence of tree-stand associated accidents was significantly reduced.

A previous study conducted nearly a decade ago at a Level I trauma center and Medical Examiner's offices in Western New York and central Maryland previously identified 51 cases of tree-stand associated injuries over a 5-year period[2]. The majority of injuries were spinal and extremity fractures. The most frequent reported reasons for falls were related to errors in placement of the stand with subsequent structural failure, and errors climbing in or out of the tree stand[2]. The need for hunter education was emphasized and the implementation of trauma prevention programs was suggested.

Our objective was to compile the current series of patients and the frequency and types of injuries they sustained. Additionally we wanted to compare our results to prior reports to identify any changes in the incidence of neurological injury related to tree stand hunting accidents.

MATERIALS AND METHODS

All tree stand-related injuries evaluated at the University of Rochester Medical Center's Emergency Department between September 2003 and November 2011 were reviewed. Information was obtained from hospital's trauma registry, and medical records were retrospectively reviewed for data pertaining to the injuries, with particular emphasis on neurological injuries and any associated details. The patients were identified based ICD-9 codes (*e.g.*, E884.9: fall from one level to another) and further review of the charts allowed us to select only falls that were sustained while hunting from a tree stand. Further data collected from the trauma registry included age, gender, Injury Severity Score (ISS), Glasgow Coma Score at the time of patient arrival, vital signs, intensive care unit (ICU) and hospital lengths of stay (LOS), procedures, and discharge disposition. The study was approved by the University of Rochester Medical Center institutional review board, and all investigators completed training in protection of human subjects.

RESULTS

A total of 54 patients were identified with tree stand related injuries during the study period. Ninety-six percent of tree-stand associated falls occurred in men. The mean age was 47.9 years (range, 15-69). The mean Injury Severity Score was 12.53 ± 1.17 (range, 2-34). The aver-

Table 1 Demographics and categorization of injuries

Metric	If not specified (n = 54)
Age (years with range)	47.9 (15–69)
Male gender	(96)
Average fall (ft with range)	18.2 (4–40)
Average length of stay	6.56 ± 1.07
Disposition	
Home	(72)
Home with services	(11)
Rehabilitation	(17)

Table 2 Reasons reported cause of falls n (%)

Reported reason	Falls (n = 13)
Tree stand construction	3 (23)
Loss of balance	3 (23)
Falling asleep	3 (23)
Structural failure	2 (15)
Lightheadedness	1 (8)
Other	1 (8)

age height of fall was 18.2 feet (range, 4-40 feet) (Table 1). No correlation could be drawn from records between height of the fall and the severity of the injuries. All patients fell to the ground with exception of one patient falling onto rocks, and many hit the tree or branches on the way down. There were no patient deaths related to tree stand falls. The direct mechanism contributing to the fall were documented in only 13 patients, and included tree stand construction (3 patients), loss of balance (3 patients), falling asleep (3 patients), structural failure (2 patients), safety harness breaking (3 patients) or "lightheadedness" (1 patient) (Table 2).

The most common injuries sustained were spinal fractures (54%). In these patients, fractures to the cervical spine were the most common (69%), followed by the thoracic (38%) and lumbar (21%) spine. These injuries included burst fractures, compression fractures, dislocations, and spinal cord transections. One patient sustained injuries resulting in immediate C5 quadriplegia, while another was paraplegic. Eight patients went to the operating room for fusion (Table 3). The remaining patients were treated nonoperatively with bracing and pain control.

The tree stand falls resulted in head injuries in 22% of patients (Table 3). Five patients suffered from facial lacerations. In addition, seven patients experienced loss of consciousness throughout the course of injury.

Thoracic injury was a common injury in many of the patients in this group. Pulmonary contusion was noted in four patients (7%). In 10 cases, patients developed a pneumothorax or hemothorax (19%), and eight of these patients were treated with a chest tube (Table 4). The other associated non-neurological injuries include injuries to the thorax such as rib/clavicle fractures (47%), pelvic fractures (11%), and abdominal solid organ injury involving lacerations to the liver, spleen, or kidney (23%) (Table 4).

Table 3 Neurological injuries resulting from tree stand falls

Injury	Patients (n = 54)
Spinal column	(54)
Cervical spine	(69)
Thoracic spine	(38)
Lumbar spine	(21)
Requiring surgery	(15)
Cranial vault/brain	(22)

Table 4 Non-neurological injuries resulting from tree stand falls n (%)

Injury	Patients (n = 54)
Orthopedic	
Upper extremity	10 (19)
Lower extremity	13 (24)
Hip/pelvis	6 (11)
Abdominal	
Liver	2 (4)
Kidney	3 (6)
Spleen	5 (9)
Other	2 (4)
Thoracic	
Pulmonary contusion	4 (7)
Pneumo-/hemothorax	10 (19)
Rib fractures	22 (41)
Clavicle fracture	3 (6)
Scapula fracture	1 (2)
Sternal fracture	3 (6)

Patients endured extremity fractures in 54% of the cases. The common injuries included fractures of the lower extremity affecting the tibia, fibula, foot, and ankle (24%), upper extremity affecting the humerus, radius, and ulna (19%), and hip and pelvis (11%) (Table 4). Fourteen patients went to the operating room for repair of extremity fractures.

The average hospital LOS was 6.56 ± 1.07. One patient required ICU care for 3 d. The discharge plans were home (72%), home with services (11%), and rehabilitation placement (17%) (Table 1).

DISCUSSION

Hunting in the American outdoors remains a unique and popular recreational activity for all ages during various times of the year. A myriad of game animals (*e.g.*, rabbit, pheasants, deer, *etc.*) are hunted with a variety of weapons from bows to shotguns or rifles[9]. Hunters have become increasingly savvier in their techniques to evade detection from their prey; one tool has been the use of tree stands or elevated platforms. Tree stands have given hunters an advantage of wider visibility without revealing their position by sight or scent[2,3]. However, with this advantage comes the increased risk of injury associated with falls during the use of these stands. The tree stands may be difficult to carry, offer minimal room for movement, and do not protect against poor weather[10]. Tree stands are typically located 15 to 30 feet above ground and can be

attached to the tree by nails, locks, or straps. The patients in our study fell from a similar height (mean fall height of 18.2 feet). As these individuals fall, the impact surface of their landing can be on hard surfaces, logs, and parts of hunting equipment adding another factor to the injury[5].

One particular study outlines that the duration of the impact force from the nature of the surface is the most important predictor of injury severity[3]. Several other studies in the literature report serious injuries related to tree stand fall[2-8]. By and large, the incidence of tree stand falls and related injuries has become one of the leading causes of hunting-related incidents. This information debunks the popular misconception that intoxicated hunters sustain self-inflected ballistic injuries as a leading cause of hunting-related incidents. In 2010, Crockett *et al*[5] discovered that 50% of the patients in their series sustained falls from tree stands compared to 29% that endured gunshot wounds in central Ohio. In our study we sought to characterize a current series of patients and compare them to prior reports in order to identify any changes in the incidence of neurological injury related to such hunting accidents. These efforts would help highlight areas to prevent the dangerous injuries from tree stand falls and improve patient safety measures through education.

There are several types of tree stands available. Some are made by commercial manufacturers using metal materials and others are homemade by hunters using wood. Only stands approved by the Tree Stand Manufacturers Association should be used, as many of the homemade types are discouraged due to deterioration of wood over time[11]. The Tree Stand Manufacturers Association (TMA), a group of corporations organized for the promotion of safe hunting practices, estimates millions of tree stand units are sold each year in the United States. One limitation of our study is that the type of tree stand used by our patients was not information available to us.

We identified 54 cases of tree stand related injuries over an 8-year period at the University of Rochester Medical Center. Our result remains consistent with the previous study done at this trauma center that detected 27 cases over a 5-year period[2]. Our current study observed that tree stand falls continues to make up a significant portion of hunting related accidents. Consequently, prior efforts to reduce the morbidity and mortality associated with tree stand falls have not been successful. This evidence suggests that tree stand safety must remain a priority for hunters and health care providers. The most common mechanisms of the injury pattern noted in our study were due to tree stand construction, structural failure, loss of balance, falling asleep, structural failure, and the safety harness breaking. In some cases patients were unsure of how they had fallen as some were amnestic to the incident. All of these contributing factors of injury indicated that further instruction is required in New York State to ensure the safety of licensed hunters. New York requires a mandatory hunter education course for a minimum 10 h in length[12]. While hunters are mandated to take a course, we recommend stronger measures to ensure hunters acquire the information needed to safely operate tree stands (*e.g.*, periodic testing of proper use by Safety Course instructors).

Due to the large number of patients injured as a result of preventable causes, an educational safety course is warranted and further instruction to hunters is necessary to ensure more compliance with these guidelines. During these Hunter's Safety Courses offered by the state or county governments the quantity and severity of these neurological injury patterns, extended hospitalizations, and permanent disability needs to be addressed in more length to provide greater awareness. Additional instruction on adherence to the regulations while hunting should be emphasized; for example, the need to exercise extreme precaution when entering or exiting the tree stand, and the need to wear a safety harness at all times. Emphasis on proper techniques need to be made to ensure hunters pay more attention when they hoist or lower items from the tree stand in a safe manner. Hunters should avoid hunting when fatigued, use communication devices, restrict alcohol or drug while hunting, hunt in groups, and only hunt during times specified by local or state regulations.

Active awareness to hunters has been proven to reduce the incidence of tree stand related trauma. In Louisiana, letters were sent to licensed hunters, hunting clubs, sporting goods stores, and hunting supply retailers across the state that detailed the risks associated with tree stand use without a safety device[3,8,13]. In the 3 years following this active awareness campaign, there were no spinal cord injuries from tree stand related incidents. Rochester, NY and other areas with active tree stand hunters will greatly benefit from similar campaign efforts.

Tree stand manufacturers add specific guidelines to the products they produce and encourage the strict use of wearing a full body safety harnesses[14]. Review of the medical records at Strong Memorial Hospital did not include information regarding safety harnesses. This may be due to recall bias from post-concussive amnesia, or insufficient information surrounding the circumstances of the injury. However prior studies have specifically documented the lack of a safety harness as a contributing mechanism[2,3], and we speculate that the absence of this information may suggest these safety devices were not used.

Injuries sustained from tree stand falls often require operative or other interventions that can increase the total cost to the healthcare system[7]. In an era where healthcare costs are carefully monitored, any preventive efforts that can reduce the overall cost of care and diminish the long-term costs for permanently disabled patients should be investigated and pursued. Additionally early identification of injured patients and a thorough assessment of their injuries are critical to improving outcomes[3]. Though it is tempting to focus on the intracranial and spinal pathologies, non-neurological injuries must not be minimized in the evaluation of these types of patients as tree stand falls do result in significant thoracic, abdomi-

nal, and pelvic trauma. A complete trauma assessment must be performed for each patient and all injuries thoroughly documented and treated in a timely fashion.

While we attempted to catalogue and describe the incidence of all tree-stand related injuries, our work is not without limitations. First, while all injuries that were deemed by the injured party or their associates were brought for hospital evaluation, it is reasonable to assume that hunters who sustained injuries may have declined to seek medical attention. The lack of any obvious trauma following a fall also may have prevented hunters from evaluation. Our series also does not capture those patients who sustained injuries at regional, community hospitals but whose injuries were not severe enough to warrant transfer to our facility. Lastly, while a thorough search for all patients was attempted, using ICD-9 codes as an initial filter may have missed patients whose diagnoses were not accurately documented at the time of their presentation.

From an international standpoint, hunting, as both a source of food and recreation, has been enjoyed by civilizations for thousands of years. Indian emperors would routinely employ elephants to hunt for wild game, and European monarchs often enjoyed fox and boar hunting as a sport while on horseback. However, from our search, tree stands appear to be a more modern invention that are primarily used in North America. Literature searches yielded no published data on hunting accidents outside of North America, and most international hunting and safety organizations focus their attention to this area as well.

In light of this data, more awareness and education are sorely needed. To this end, the authors have utilized the findings from this paper in local print and television media to educate the local community on the continued prevalence of tree stand injuries. A campaign has been initiated in New York to better educate hunters, with the aim of formally incorporating this study's findings in novel educational material for the New York State hunter safety educational curriculum.

Hunting remains an attractive recreational activity and the methodical use of tree stands have made hunters more effective at game hunting. This study reveals that nearly 10 years later, tree stand falls remain a significant cause of life-threatening neurological injury and subsequent disability. Increased awareness by healthcare providers and implementation of prevention strategies is critical to reducing the incidence of injuries sustained while hunting with tree stands. These prevention strategies can be taught during hunter safety education courses. All hunters should be made aware of the preventable risk factors that contribute to injury (structural failure, fatigue, lack of sleep, and drug and alcohol use). Additionally, hunters should be licensed and properly educated on the safe and proper use of tree stand and associated equipment (*e.g.*, safety harness), and ensure that equipment is in proper working condition on a routine basis. Tree stand manufacturers can aid in these hunter education prevention programs by giving more support to efforts for the hunter's safety. Health care providers can also aid safety and education efforts, as physicians who treat these hunters may advocate for these prevention efforts to reduce incidence of neurologic injury during hunting.

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COMMENTS

Background

The role of tree stands in hunting accidents has been investigated to determine the incidence of injuries involving these devices. This study also compared current data with data obtained nearly a decade ago to identify any trends that have changed.

Research frontiers

Neurotrauma, public health.

Innovations and breakthroughs

Despite improvements in medical care, tree stand injuries continue to occur with no real abatement in incidence. Other states have instituted public health campaigns to educate hunters of the risks and these efforts have reduced rates of injury.

Terminology

Tree stands are devices used by hunters to give them a seat at an elevated position in a tree to observe wild game.

Peer review

This is a well-written study on hunting related injuries due to tree stand falls. The topic is interesting, important, and not sufficiently researched and the findings will hopefully raise awareness on safety issues. The study is well-designed and the findings are adequately presented. The discussion is balanced and informative.

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RETROSPECTIVE STUDY

Intracerebroventricular opiate infusion for refractory head and facial pain

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Abstract

AIM: To study the risks and benefits of intracerebroventricular (ICV) opiate pumps for the management of benign head and face pain.

METHODS: SSix patients with refractory trigeminal neuralgia and/or cluster headaches were evaluated for implantation of an ICV opiate infusion pump using either ICV injections through an Ommaya reservoir or external ventricular drain. Four patients received morphine ICV pumps and two patientS received a hydromorphone pump. Of the Four patients with morphine ICV pumps, one patient had the medication changed to hydromorphone. Preoperative and post-operative visual analog scores (VAS) were obtained. Patients were evaluated post-operatively for a minimum of 3 mo and the pump dosage was adjusted at each outpatient clinic visit according to the patient's pain level.

RESULTS: All 6 patients had an intracerebroventricular opiate injection trial period, using either an Ommaya reservoir or an external ventricular drain. There was an average VAS improvement of 75.8%. During the trial period, no complications were observed. Pump implantation was performed an average of 3.7 wk (range 1-7) after the trial injections. After implantation, an average of 20.7 ± 8.3 dose adjustments were made over 3-56 mo after surgery to achieve maximal pain relief. At the most recent follow-up (26.2 mo, range 3-56), VAS scores significantly improved from an average of 7.8 ± 0.5 (range 6-10) to 2.8 ± 0.7 (range 0-5) at the final dose (mean improvement 5.0 ± 1.0, $P < 0.001$). All patients required a stepwise increase in opiate infusion rates to achieve maximal benefit. The most common complications were nausea and drowsiness, both of which resolved with pump adjustments. On average, infusion pumps were replaced every 4-5 years.

CONCLUSION: These results suggest that ICV delivery of opiates may potentially be a viable treatment option for patients with intractable pain from trigeminal neuralgia or cluster headache.

Key words: Intracerebroventricular; Opiate; Trigeminal neuralgia; Cluster headache; Pain

Core tip: Chronic head and face pain remains a debilitating condition, and patients may often be refractory to traditional medical therapies or surgical intervention (*i.e.*, stereotactic radiosurgery or microvascular decompression). Alternatively, the use of intracerebroventricular (ICV) pain pumps has been used for refractory nociceptive pain from head and neck cancer; however, its use in non-cancer head and face pain has not been well described. Here, we report the potential risks and benefits of ICV opiate pain pumps for cluster headaches and trigeminal neuralgia refractory to medical and surgical treatment.

Lee DJ, Gurkoff GG, Goodarzi A, Muizelaar JP, Boggan JE, Shahlaie K. Intracerebroventricular opiate infusion for refractory head and facial pain. *World J Clin Cases* 2014; 2(8): 351-356 Available from: URL: http://www.wjgnet.com/2307-8960/full/v2/i8/351.htm DOI: http://dx.doi.org/10.12998/wjcc.v2.i8.351

INTRODUCTION

Chronic head and face pain is a debilitating condition that affects over 3%-5% of people worldwide[1], dramatically impacting emotional, psychological, and economic well-being. Two common etiologies of severe head and face pain are cluster headache and trigeminal neuralgia, which affect 300000 and 100000 people in the United States, respectively. Cluster headache is typically managed with medical therapies or botox injections[2,3], and most cases of trigeminal neuralgia are successfully treated with oral medications, stereotactic radiosurgery, or microvascular decompression[4]. However, 5% of patients with cluster headache[5] and 11%-25% of patients with trigeminal neuralgia[6-10] do not achieve adequate pain relief with these therapies and may require other treatment options.

Neurosurgical treatment options for pain syndromes have generally focused on modulation of specific pain pathways by lesioning, electrical stimulation, or spinal intrathecal delivery of pharmacological agents[11,12]. Targets for electrical neuromodulation include the dorsal columns of the spinal cord, the sensory nuclei of the thalamus, the precentral motor cortex for neurogenic/neuropathic pain, and the periventricular/periaqueductal gray area for somatic or nociceptive pain[13]. Chemical neuromodulation *via* central delivery of pharmacological agents is primarily accomplished *via* spinal intrathecal delivery strategies[14].

Intracerebroventricular (ICV) administration of opioids represents a chemical, rather than electrical, neuromodulation treatment strategy. This allows for drug delivery directly at its anatomical site of action, achieving high tissue concentrations of drug that would not be achievable with systemic drug delivery. ICV delivery of opiate medications has been previously described for management of refractory nociceptive pain from head and neck cancer[15-19]. This is typically accomplished *via* intermittent injection of opiates into an Ommaya reservoir[17,20-22], although use of an implanted infusion pump has also been reported[19,23]. In this study, we present our institutional experience treating six patients with ICV opiate pain pumps for treatment of severe, refractory head and face pain due to cluster headache and/or trigeminal neuralgia.

MATERIALS AND METHODS

Patient population

Six adult patients (4 women, 2 men) underwent implantation of an ICV opiate pump into the right lateral ventricle for treatment of severe, refractory head and/or face pain at the University of California, Davis Medical Center. The average age of symptom onset was 44.3 years (range 17-75), the average duration of symptoms was 14.8 years (range 4-31), and the average age at ICV implantation was 59.0 years (range 35-79). Four patients had facial pain, 1 patient had cluster headaches, and 1 patient had cluster headache and atypical facial pain. Patients had trialed an average of 4 (range 1-9) oral pain medications prior to ICV implantation; 2 patients trialed opiate injection therapy, 2 patients had failed microvascular decompression for facial pain, and none of the patients in this series had undergone previous radiosurgery for pain (Table 1). The University of California, Davis Institutional Review Board approved this retrospective study.

Treatment protocol

Prior to ICV opiate pump implantation, all patients demonstrated significant clinical benefit with trial injection of opiates through an Ommaya reservoir (n = 5) or an external ventricular drain (EVD, n = 1). Trial injections were performed in the neurosurgical intensive care unit for close monitoring of known complications of ICV opiate delivery, including mental clouding, visual hallucinations, seizures, somnolence, respiratory depression, and coma[24]. Initially, patients underwent a trial injection phase (3-15 d) at which time the dose of morphine or hydromorphone was titrated to determine an optimal dose for each individual. A Medtronic (Minnesota, United States) pain pump was implanted into a subcutaneous fat space in the abdomen within one month of the trial injections by one of two neurosurgeons (J.E.B, K.S.). In one patient (patient 6), intraoperative computed tomography was used to confirm placement of the intraventricular catheter (Figure 1). Adjustment of dose rates and/or refilling of pumps occurred monthly.

Outcome assessment

Visual analogue scale (VAS) scores were obtained before and after intraventricular trial injections, and before and after the ICV opiate pump infusion began. VAS scores were collected on an intermittent basis during outpatient clinic visits, before and after infusion rate adjustments.

RESULTS

There were no complications associated with placement of an Ommaya reservoir or EVD to perform trial injections. During trial injection therapy, one patient experienced a transient side effect of nausea but there were no permanent complications. An average of 9.2 doses (range 2-27) was necessary during the trial phase to provide maximum VAS improvement with trial injections (average VAS improvement 75.8%, range 50%-100%).

Pump implantation was performed an average of 3.7 wk (range 1-7) after ICU trial injections had been completed, and patients required an average of 20.7 (range 2-51) outpatient adjustments to the dose. At the most recent follow-up (26.2 mo, range 2-56, one patient transferred care to a different institution), VAS pain scores significantly im-

Table 1 Patient characteristics and outcomes

Patient	Age (at pump placement, yr)	Gender	Primary diagnosis	Prior surgeries	Pre-implantation trial	ICV pump medication	Initial dose (mg/d)	Final dose (mg/d)	Pre-op VAS	Post-op day 1 VAS	Last VAS	Last post-op visit (mo)
1	67	Male	Trigeminal neuralgia (left)		Ommaya reservoir-morphine	Morphine then dilaudid	0.1 morphine	3.27 dilaudid	6	3.5	4	145
2	35	Female	Cluster headaches		Ommaya reservoir-morphine	Morphine	0.65 morphine	19.0 morphine	8	4	0	166
3	37	Female	Trigeminal neuralgia (right), Cluster headaches		Ommaya reservoir-morphine, dilaudid	Dilaudid	0.1 dilaudid	0.2 dilaudid	8	2.5	3	9
4	74	Male	Trigeminal neuralgia (left)	Rhizotomy, Microvascular decompression	Ommaya reservoir-morphine	Morphine	0.75 morphine	1.75 morphine	8	1	1	10
5	62	Female	Trigeminal neuralgia (right)	Microvascular decompression	Ommaya reservoir-morphine	Morphine	4 morphine	4.25 morphine	10	3	2	3
6	79	Female	Trigeminal neuralgia (left)	Meningioma resection (left), radiosurgery ×2	External ventricular drain-morphine, dilaudid	Dilaudid	0.01 dilaudid	0.085 dilaudid	8	2	2	15

VAS: Visual analogue scale; ICV: Intracerebroventricular.

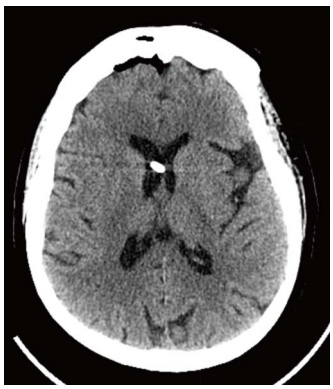

Figure 1 Intraoperative computed tomography of the head demonstrates intraventricular placement of the pump catheter (Patient 6).

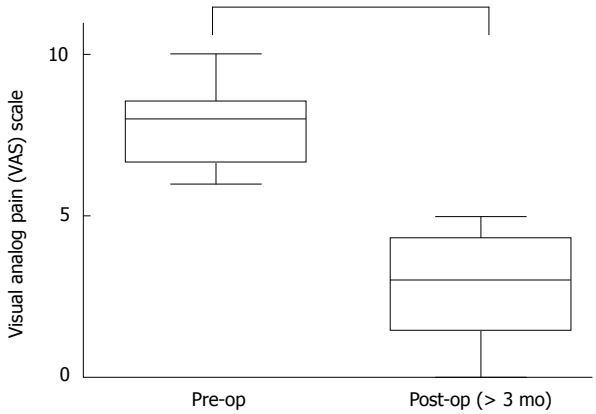

Figure 2 Preoperative visual analogue scale pain scores ranged from 6-10 out of 10 (average 7.8 ± 0.5). Post-operative visual analogue scale (VAS) scores at > 3 mo following opioid pain pump placement were significantly lower ($P < 0.001$ *vs* Post-op), ranging 0-5 out of 10 (average 2.7 ± 0.4).

proved from an average of 7.8 ± 0.5 (range 6-10) to 2.8 ± 0.7 (range 0-5) once reaching final dose (mean improvement 5.0 ± 1.0, $P < 0.001$, Table 1, Figure 2).

All patients required stepwise increases in infusion rates to achieve maximal benefit. The average initial morphine dose was 1.4 mg/d (range 0.1-4.0 mg/d) and the average final dose was 11.7 mg/d (range 2-21.5, $n = 4$). The average initial hydromorphone dose was 0.08 mg/d (range 0.01-0.2 mg/d) and the average final dose was 1.2 mg/d (range 0.1-3.3). In one patient (Patient 1), the medication was changed from morphine to hydromorphone to achieve maximal benefit; in this patient, 12 morphine dosage adjustments were made prior to converting to hydromorphone 15 mo after implantation. The final morphine dosage was 21.5 mg/d and the initial hydromorphone dosage was 2.1 mg/d. Following medication adjustment, an additional 12 adjustments with hydromorphone were made. On average, infusion pumps were replaced every 4-5 years.

The most common complications in this series were nausea ($n = 2$) and drowsiness ($n = 2$), both of which resolved with adjustments in pump settings (Table 2). One patient experienced withdrawal symptoms due to pump failure, and underwent a distal catheter revision (to clear an obstruction) with subsequent resolution of her symptoms. One patient experienced psychiatric irritability after 10 years of good pain relief and had the ICV pain pump removed.

Table 2 Dose ranges and complications

Patient	Dose range (mg/d)	Complications
1	0.10-21.5 (morphine)	Nausea/Emesis (transient-decreased dosage)
	2.10-3.27 (dilaudid)	Changed medication due to inadequate pain control/nausea
2	0.65-19.0 (morphine)	Replacement of pump × 2 (q5 yr)
		Withdrawal symptoms (transient)
3	0.20 (dilaudid)	Psychiatric disturbances leading to removal of pain pump after 11 yr
4	0.75-2.0 (morphine)	Nausea/ Emesis (transient- decreased dosage)
5	4.00-4.25 (morphine)	Lost to follow-up after 1 yr
6	0.01–0.10 (dilaudid)	

DISCUSSION

ICV opiate infusion using an implanted pump provides significant pain relief in patients with severe, refractory head and/or face pain that have failed other medical and surgical therapies. This study adds to the existing literature on successful use of ICV opiates for management of head and neck cancer pain[25], and suggests that ICV opiate infusion may be a prudent treatment option for select patients with severe cluster headache or trigeminal neuralgia.

While the mechanism and site of action of opioids in the brain for head and neck pain is not completely understood, it is known that morphine and its derivatives bind to receptors that are found in the periventricular and periaqueductal gray regions, medulla spinalis, substantia gelatinosa, and the hypothalamus[13,26-30]. Therefore, it is possible that ICV delivery of opioids selectively modulates activity in these brain regions, resulting in a level of analgesia that may be superior to that achieved with systemic therapies.

The efficacy of deep brain stimulation (DBS) of the periventricular/periaqueductal gray region for management of cluster headache and other central pain syndromes[11,13,26] supports the hypothesis that targeted delivery is effective for refractory cases. Due to its proximity to pain pathways in the brainstem, hypothalamus, and thalamus, ICV delivery may potentially be more prudent than intraspinal intrathecal delivery for severe, refractory head and face pain syndromes. Prospective comparative studies are needed to further explore this possibility.

Because the pathophysiology of refractory trigeminal neuralgia and cluster headaches are poorly understood, ICV infusion therapy may be more effective than DBS since its effects are more regional and affect a larger volume of tissue. Different brain areas have been implicated in refractory cluster headache[31,32], and the anatomical basis of trigeminal neuralgia that fails medical therapy and microvascular decompression is often elusive and has been attributed to demyelination or other unknown processes. Various lesioning therapies have been proposed for failed microvascular decompression, including therapies that target the facial nerve (chemical, mechanical decompression, radiosurgery, and nerve cutting) or its brainstem pathways (nucleus caudalis dorsal root entry zone lesioning). Since these procedures are irreversible and can carry significant risks, ICV opioid infusion may be a preferable alternative since it allows for delivery of a regional targeted therapy that can be titrated to effect and, if necessary, discontinued.

It is important to note that cluster headache and trigeminal neuralgia are very different disorders with unique clinical and pathological characteristics. For example, cluster headaches are far more common in men (8:3 ratio)[33] whereas trigeminal neuralgia affects more women than men (3:2 ratio)[34]. Since morphine is generally more potent in men than women, it is possible that different opioid infusion strategies are needed to achieve adequate analgesia in these conditions. Such differences were not evident in the current series, but larger clinical studies are needed to determine if gender-specific and/or disease-specific opioid infusion strategies will yield better clinical outcomes.

The risks associated with ICV opiate infusion therapy include neurological injury from ventricular catheter placement, implant infection, and opioid toxicity (including allergy, intolerance or significant clinical side effects). We recommend a trial therapy in an ICU setting prior to pump implantation to confirm clinical efficacy and evaluate for any signs of opioid toxicity. After implantation, a slow, step-wise titration of opioid infusion is recommended to achieve maximum clinical efficacy with minimal side effects and complications. In this series, the average number of dose adjustments was 20.7 (range 2-51). The high number of adjustments demonstrates that opioid tolerance can develop over time. Special consideration should be given to the development of opioid tolerance and the risks associated with abrupt disruption or withdrawal of therapy (in the setting of pump failure, for example). There is some evidence that co-administration of drugs may enhance analgesia and reduce the likelihood of tolerance. For example, pre-clinical animal studies suggest that co-administration of drugs like calmodulin inhibitors[35,36] or inhibitors of protein kinases[37] may reduce or prevent morphine tolerance from developing. Also, there is evidence that certain non-opioid medications, such as the voltage-gated calcium channel blocker ziconotide, are extremely effective when delivered as an intrathecal infusion[38,39] and may be appropriate alternatives to opioids or effective in a co-administration strategy.

In conclusion, severe head and facial pain syndromes that are refractory to conventional medical and surgical

therapies can be extremely debilitating and very difficult to manage. ICV opioid infusion has the potential to enhance analgesia through regional delivery of drug to brain centers that are directly responsible for processing pain signals. Using a careful clinical protocol to screen for efficacy and reduce risks, ICV opioid infusion therapy may be an effective treatment option for patients with severe head and facial pain due to cluster headache and trigeminal neuralgia.

COMMENTS

Background

Intracerebroventricular (ICV) opiate pumps are used for management of chronic pain due to head and neck cancers, but their use for neurological etiologies of benign head and face pain has not been well studied. This study aims to evaluate the risks and benefits of intracerebroventricular opiate pumps for management of benign head and face pain.

Research frontiers

Here, the authors describe the use of intracerebroventricular pain pumps for benign head and face pain refractory to medical and/or surgical treatment. While neurosurgical options for pain include lesioning, electrical stimulation, or spinal intrathecal delivery of pharmacological agents, the use of intracerebroventricular opiates has not been well described.

Innovations and breakthroughs

While intracerebroventricular pain pumps have been used for head and neck cancer pain, its use for benign head and face pain, such as trigeminal neuralgia or cluster headaches, has not been well described. This study suggests that ICV pain pumps may be a potential treatment option for patients suffering from benign head and face pain refractory to medical and/or surgical treatments.

Applications

This study suggests that intracerebroventricular pain pumps may be a viable option for patients with benign head and face pain that are refractory to previous medical or surgical treatments. Randomized controlled trials would need to be performed to further evaluate the efficacy and safety of this modality.

Terminology

Intracerebroventricular pain pump: Opiates can be administered into the ventricles directly *via* this modality. This can be distinguished from spinal catheter pain pumps. Visual analog score: 10-point pain scale used to evaluate severity of pain (0: no pain, 10 most severe pain).

Peer review

Interesting clinical article on intracerebroventricular opiate infusion for refractory head and facial pain. The authors report on a cohort of 6 patients with refractory trigeminal neuralgia and/or cluster headaches which underwent implantation of an intracerebroventricular opiate infusion pump as a means to control intractable pain. The article is well written, the patient population is presented in detail and the same applies to treatment protocol and outcome assessment. The results are equally presented with clarity and the discussion includes up to date references that correlate with the authors clinical results.

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CLINICAL TRIAL STUDY

Distal biceps tendon rupture reconstruction using muscle-splitting double-incision approach

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Abstract

AIM: To evaluate the clinical and functional results after repair of distal biceps tendon tears, following the Morrey's modified double-incision approach.

METHODS: We retrospectively reviewed 47 patients with distal rupture of biceps brachii treated between 2003 and 2012 in our Orthopedic Department with muscle-splitting double-incision technique. Outcome measures included the Mayo elbow performance, the DASH questionnaire, patient's satisfaction, elbow and forearm motion, grip strength and complications occurrence.

RESULTS: At an average 18 mo follow-up (range, 7 mo-10 years) the average Mayo elbow performance and DASH score were respectively 97.2 and 4.8. The elbow flexion range was 94%, extension was -2°, supination was 93% and pronation 96% compared with the uninjured limb. The mean grip strength, expressed as percentage of respective contralateral limb, was 83%. The average patient satisfaction rating on a Likert scale (from 0 to 10) was 9.4. The following complications were observed: 3 cases of heterotopic ossification (6.4%), one (2.1%) re-rupture of the tendon at the site of reattachment and 2 cases (4.3%) of posterior interosseous nerve palsy. No complication required further surgical treatment.

CONCLUSION: This technique allows an anatomic reattachment of distal biceps tendon at the radial tuberosity providing full functional recovery with low complication rate.

Key words: Distal biceps tendon; Rupture; Double incision; Complications; Clinical outcome; Trans-osseous tunnels; Morrey

Core tip: Both single and double-incision approaches have been successfully used for distal biceps tendon lesions. At present there is no solid scientific evidence to support preference of one technique over the other. However, recently, it has been demonstrated that the 2-incision technique recreates more closely footprint position compared with that of the 1-incision approach. In the present research the Morrey's modified double-incision repair provided excellent outcome (including functional outcome, satisfaction, elbow and forearm motion, and grip strength) with few post-operative complications, mainly represented by heterotopic ossification and posterior interosseous nerve injuries.

Tarallo L, Mugnai R, Zambianchi F, Adani R, Catani F. Distal biceps tendon rupture reconstruction using muscle-splitting double-incision approach. *World J Clin Cases* 2014; 2(8): 357-361 Available from: URL: http://www.wjgnet.com/2307-8960/full/v2/i8/357.htm DOI: http://dx.doi.org/10.12998/wjcc.v2.i8.357

INTRODUCTION

The incidence of distal biceps ruptures is estimated between 0.9 and 1.8 per 100000 population per year, and accounts for 3% of biceps brachii tendon injuries[1]. This injury is very common in men who are in their fifth or sixth decade of life, but can also occur at any age[2-4].

Many studies demonstrated that surgical approaches allow better clinical results than conservative treatments[5,6]. In literature, various surgical methods have been described, dating back to the first report by Acquaviva in 1898[7,8].

In 1956 Fischer *et al*[9] used the volar Henry approach to reattach the distal biceps tendon to the radial tuberosity. This allowed a good recovery of flexion and supination strength, but radial nerve palsy occurred in several cases consequently to the extensive exposure needed using this approach[10,11].

To decrease the risk of neurologic complications limiting the exposure needed Boyd *et al*[12] in 1961 described a two-incision technique to access the tuberosity more easily. They felt that a second dorsal incision was necessary in order to limit the volar surgical dissection required near the radial nerve as it passes through the supinator muscle[13-15]. However, complications with special respect to heterotopic ossifications including loss of forearm rotation, radioulnar synostosis, and posterior interosseous nerve injury were described using the double-incision technique[16,17].

In an effort to overcome any complications connected with each approach, more modern techniques have been developed in the last decades. The two-incision approach was updated by Morrey *et al*[18], who used a posterior muscle-splitting approach that avoids subperiosteal exposure of the ulna, and therefore reduces the possibility of radioulnar synostosis. With this adjustment, the tendon can be reattached to the radial tuberosity through transosseous drill holes.

More recently approaches that use suture anchors and a limited single anterior incision have been described[11,19,20]. Currently there is no consensus with respect to the best surgical approach and favorable results with both techniques[21-23].

The aim of our study is to evaluate the clinical and functional outcomes after surgical repair of distal tendons tears, using a muscle-splitting double incision approach modified by Morrey[18].

MATERIALS AND METHODS

This study has been authorized by the local ethical committee and was carried out in accordance with the Ethical standards of the 1964 Declaration of Helsinki as updated in 2004. We retrospectively reviewed 47 patients operated by two different surgeons of distal rupture of biceps brachii, treated in our Orthopedic Department between March 2003 and September 2012 using the muscle-splitting double-incision technique. Every patient undergoing distal biceps tendon acute rupture repair, was included in our review and informed consent was obtained. Exclusion criteria included the presence of an associated fracture, and dislocation about the elbow as etiology of biceps injury. All patients included in our cohort were treated within 15 d from trauma. We analyzed the rate of major and minor complications. Major complications included posterior interosseous nerve (PIN) palsy, heterotopic ossification and re-rupture. Minor complications included superficial infection, lateral antebrachial cutaneous nerve paresthesia and radial sensory nerve paresthesia. All 47 cases are men, with an average age of 45 (range, 28-66 years) at the time of injury. The dominant arm was involved in 43 patients, 91% of all cases. The injury mechanism was the same in every case: an eccentric load applied to a flexed elbow during daily or sport activity. Subjective outcomes included the Disability of Arm, Shoulder and Hand (DASH) questionnaire and the Mayo elbow performance score. In addition, levels of overall patient satisfaction were determined using a 10-point scale: in which 10 points denoting very satisfied and 1 point denoting very unsatisfied. All measurements were performed at an average 18 mo follow-up (range, 7 mo-10 years) by an independent assessor who measured elbow and forearm motion using a goniometer.

All patients underwent the same surgical method: the double incision technique uses a transverse incision in the antecubital fossa. After identification of the distal portion of the biceps tendon, the degenerated part is resected. Two locking Krackow sutures with N.2 fiber-wire (Arthrex, Naples, FL) are passed through the distal part of the tendon. After bicipital tuberosity identification, a curved clamp is lead through the interosseous space, forceps are then palped on the dorsal aspect of the proximal part of the forearm, and second longitudinal incision is made over it. With the forearm in maximal pronation, the tuberosity is exposed with a muscle-splitting technique. Three drill holes are placed approximately at 1 cm intervals through the dorsal cortical margin of the tuberosity. The tendon sutures are then passed through the holes. With the elbow at 90° of flexion and the forearm pronated, the biceps tendon is pulled into the bicipital tuberosity and sutures are pulled tight and tied (Figure 1). The elbow is then splinted for 4 wk. Early active-assistive and ROM activities into elbow flexion and extension are advised 3-4 times per day. All patients were treated with indomethacin 75 mg for 3 wk as a standard protocol to prevent heterotopic ossifications.

RESULTS

The average elbow flexion range was 94% of the uninjured limb (125° *vs* 135°). Average extension was -2°. Supination was 93 % and pronation 96% compared with the uninjuried limb (supination 80° *vs* 84°; pronation 86° *vs* 82°) (Figure 2). The average Mayo elbow performance and DASH score were respectively 97.2 and 4.8. The satisfaction rating score was 9.4 points (Table 1).

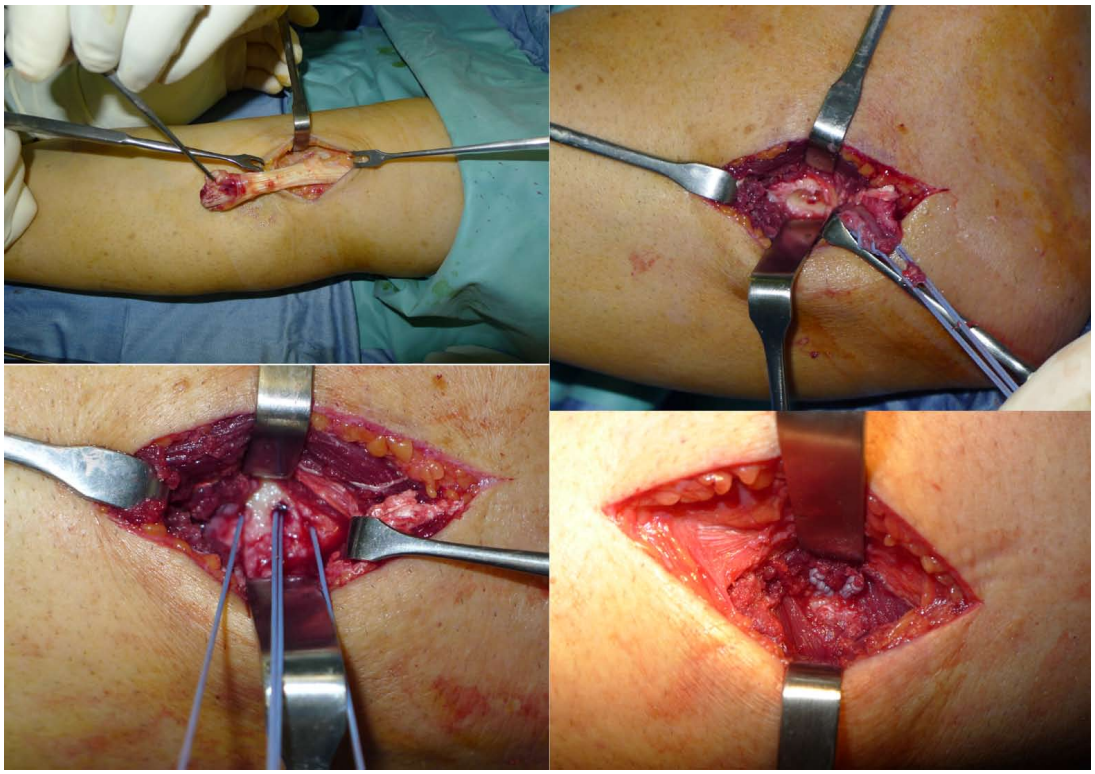

Figure 1 Intraoperative view showing the double access and the surgical procedure.

Figure 2 Clinical evaluation at 40 d after surgery showing complete recovery of the range of motion.

The reported complications included nerve dysfunction, heterotopic ossification and failure at repair site. We had 3 cases of heterotopic ossification with limited range of movement near to complete loss of forearm rotation. Resection of heterotopic bone was associated with restoration of near-normal motion. One re-rupture of the

Table 1 Clinical outcome and complications occurrence *n* (%)

Clinical outcome										Complications		
Range of motion								Mayo	Dash	Grip strengTH	Satisfaction	Eterotopic ossification	Tendon re-rupture	Pin palsy
Flexion (94)		Extension (97)		Pronation (93)		Supination (96)								
125 ± 8.4	94%	-2 ± 4.3	97%	80 ± 5.7	93%	82 ± 6.5	96%	97.2 ± 12.0	4.8 ± 8.2	83%	9.4 ± 5.6	3 (6.4)	1 (2.1)	2 (4.3)

Data are expressed as absolute numbers (percentage) or mean ± SD.

tendon at the site of reattachment was found. Two cases of posterior interosseous nerve (PIN) palsy were found but both were resolved without intervention (Table 1).

DISCUSSION

Distal biceps tendon ruptures usually arise in the dominant elbow of middle-aged male patients[24]. The clinical presentation is characteristic and radiographs, MRI or ultrasound are not necessary to diagnose an acute rupture of the distal biceps. In recent decades surgical repair of this type of lesions have shown improved functional outcomes compared with conservative treatment. Baker *et al*[2] compared operative and nonoperative treatment showing decreased supination strength of 55% and supination endurance of 86% with nonoperative approach compared with controls. Several surgical options have been described in literature: the one incision-approach, using suture anchor, endobuttons, biotenodesis screw for fixation and a two incision approach using bone tunnels[25]. The recreation of an anatomic reattachment of the distal biceps tendon to its osseous insertion at the radial tuberosity has to be the main objective of operative treatment. The modified two-incision approach has demonstrated excellent clinical results with regards to postoperative range of motion, strength, and endurance[26]. Distal biceps tendon repair sometimes lacks elbow motion, due to heterotopic ossification or radioulnar exostosis as well as neurological complications such as PIN injury[27]. Heterotopic bone formation is common following distal biceps tendon surgery and has been reported in both single and double-incision repairs. Higher rates of heterotopic ossification have been described in double-incision treatments performed using the Boyd-Anderson method, where the posterior soft tissues are elevated off the ulna to expose the radial tuberosity[16,17]. Radioulnar synostosis, although rare, is more common with the Boyd-Anderson method rather than with muscle-splitting double-incision approach, in which the periosteal surface of the ulna is not exposed. With this technique, the incidence of synostosis and heterotopic bone has substantially decreased[28,29]. In our cohort complications were reported in 12.8% of cases: 3 cases of heterotopic ossification (6.4%), one (2.1%) re-rupture of the tendon at the site of reattachment and 2 cases (4.3%) of PIN palsy, all of them resolved without intervention. Our rate of complications appears similar to the 10% of cases reported by El-Hawary *et al*[21] using the 2-incision technique, associated with 6-wk prophylaxis with indomethacin 25 mg 3 times a day for 6 wk. In particular they didn't observed any case of heterotopic ossification, and the only type of complication reported was a transient superficial radial nerve paresthesia, supporting a longer lasting profilaxis against heterotopic ossification.

In our research tendon fixation was performed by 3 trans-osseous tunnels placed at the apex of radial tuberosity. In the last years, new fixation equipment like suture anchors, interference screws, and fixation buttons have been brought in and biomechanically tested[30-34], demonstrating encouraging results[35-37].

Clinical studies have found little difference between 1- and 2-incision approaches in terms of complications, re-ruptures, flexion and supination strength as well as endurance[21,23,26,38]. However, recently, it has been demonstrated that the 2-incision approach recreates more closely footprint position compared with the 1-incision approach[39].

In conclusion, the Morrey's modified double-incision repair provided excellent outcome (including functional outcome, satisfaction, elbow and forearm motion, and grip strength) with few post-operative complications, mainly represented by heterotopic ossification and PIN injuries.

COMMENTS

Background

Biceps tendon ruptures occur at the distal aspect in 3% of all lesions. Both single-incision and 2-incision techniques, using various fixation methods, have been described to accomplish tendon reattachment to the bicipital tuberosity; however there is no consensus with respect to the best surgical approach.

Research frontiers

Authors retrospectively reviewed 47 patients with distal rupture of biceps brachii treated between 2003 and 2012 in authors' Orthopedic Department with muscle-splitting double-incision technique.

Innovations and breakthroughs

In the present research the Morrey's modified double-incision repair provided excellent outcome (including functional outcome, satisfaction, elbow and forearm motion, and grip strength) with few post-operative complications, mainly represented by heterotopic ossification and posterior interosseous nerve injuries.

Peer review

The article is interesting, well written, documented and analyzed with tests valid and internationally recognized. Good and clear figures. The discussion and conclusions interesting and valid. The author think it can be published with high priority.

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OBSERVATIONAL STUDY

Dabigatran etixilate and traumatic brain injury: Evolving anticoagulants require evolving care plans

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Abstract

AIM: To investigate the outcomes of trauma patients with traumatic brain injury (TBI) on Dabigatran Etexilate (DE).

METHODS: Following IRB approval, all patients taking DE who were admitted to our level 1 trauma service were enrolled in the study. Injury complexity, length of stay (LOS), intensive care length of stay, operative intervention, therapeutic interventions and outcomes were analyzed retrospectively.

RESULTS: Twenty-eight of 4310 admissions were taking DE. Eleven patients were excluded on concurrent antiplatelet therapy. Average age was 77.14 years (64-94 years), and average LOS was 4.7 d (1-35 d). Thirty-two percent were admitted with intracranial hemorrhage. Eighteen percent received factor Ⅶ, and 22% received dialysis in attempts to correct coagulopathy. Mortality was 21%.

CONCLUSION: The low incidence, absence of reversal agents, and lack of practice guidelines makes managing patients with TBI taking DE frustrating and provider specific. Local practice guidelines may be helpful in managing such patients.

Key words: Dabigatran; Brain injury; Anticoagulation; Dabigatran reversal

Core tip: Dabigatran Etexilate (DE) and other novel anticoagulants that lack reversal agents complicate the care of trauma patients. Current practice guidelines should be available to aid in managing patients with traumatic brain injury on DE.

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INTRODUCTION

Arterial and venous thromboembolism (VTE) is a significant cause of mortality and morbidity. Direct and indirect inhibitors of coagulation are being increasingly utilized for prophylaxis and treatment of myocardial infarction, valvular disease, deep venous thrombosis, pulmonary embolism, atrial fibrillation, and stroke[1]. Compliance rates for VTE prophylaxis are being used in pay for performance by third party payors and have been included as an independent new core measure by the Center for Medicare and Medicaid Services[2].

Many anticoagulants are available to the clinician: an-

Table 1 Traumatic brain injury, non-traumatic brain injury and acute care surgery patients on Dabigatran

	TBI	nonTBI	ACS	Total
n	9	10	9	28
Age (yr)	83.4 (8.48)	73.6 (11.6)	76 (8.87)	77.14 (10.5)
M:F	4 M: 5 F	5 M: 5 F	6 M: 3 F	15 M: 13 F
INR	1.69 (0.43)	1.3[1]	1.3[1]	1.45[1]
PTT (s)	54.55 (18.09)	48.05 (33.18)	37[1]	50.35[1]
Concurrent AntiPlatelet	5	2	4	11
Hemodialysis	2	3	1	6
Factor Ⅶ	2	2	1	5
Mortality	2	1	3	6

[1]Median data was used due to outliers. TBI: Traumatic brain injury; PTT: Partial thromboplastin time.

tiplatelet agents, thromboxane A2 receptor antagonists, Adenosine Diphosphate (ADP) receptor antagonists, Protease Activated Receptor (PAR)-1 antagonists, inhibitors of initiation or propagation of coagulation, Factor Ⅸ-directed antibodies, direct and indirect Factor Xa inhibitors, factor Va and Ⅷa inhibitors, inhibitors of fibrin formation, and medications than enhance fibrinolysis[3]. Due to the complication rate, volume of distribution, delayed onset, prolonged effect, unpredictable pharmacokinetics, food and medication interactions, and frequent monitoring associated with warfarin usage, industry has focused on developing oral thrombin and Factor Xa inhibitors for patients who require long-term anticoagulation.

Dabigatran Etexilate (DE) (Pradaxa®) 150 mg twice daily is the first orally available FDA approved direct thrombin inhibitor (DTI) in the United States. Due to predictable pharmacokinetics and pharmacodynamics, limited drug-drug interaction or effect of food, and no need for coagulation monitoring, DE was introduced enthusiastically and approved for treatment of non-vavlular atrial fibrillation (AF) with a class 1 recommendation[4]. Head to head trials with warfarin showed that DE reduced the risk of stroke by more than one-half and that mortality from intracranial hemorrhage was not increased (1B)[5]. Patients on DE had a significantly higher rate of gastrointestinal bleeding and trended toward an increased number of adjudicated coronary events[5]. As no reversal agent or accurate method of measuring the clinical effect of DE exists, recommendations for patients undergoing elective surgery currently taking DE are to stop the DE 1-5 d prior to the procedure, depending on the complexity of the surgery and the patient's creatinine clearance (CrCL)[3,6,7].

Trauma patients and those with acute surgical issues frequently do not have the luxury of waiting 1-5 d for the pharmacologic effects of DE to subside. After several frustrating patient interactions that essentially involved supportive care, we hypothesized that patients taking DE admitted with traumatic injuries would have poor outcomes due to the lack of a reversal agent. We herein report our series of patients admitted to our trauma and acute care surgery service on DE, focusing on patients with traumatic brain injury (TBI), and comment on potential treatment strategies available.

MATERIALS AND METHODS

After receiving institutional board approval, all patients between October 2011 and September 2012 admitted through the emergency room to one health system's two Level 1 trauma centers were prospectively evaluated to include all patients who were actively taking DE on admission. Only patients over the age of 18 with vital signs on arrival were included in the study.

Patient management was directed by the trauma and acute care surgeon in conjunction with subspecialized physicians. Presence of traumatic brain injury on computed tomography (CT) was verified by a board certified radiologist, and demographic data, admission laboratory data including hemoglobin, prothrombin time (PT/INR), and partial thromboplastin time (PTT), patient acuity, therapeutic interventions, transfusion requirements, and patient outcomes were evaluated retrospectively.

Statistical analysis

Statistical analysis was performed using Microsoft Excel Analysis ToolPak (Student *t*-Test, χ^2 Test, Anova).

RESULTS

Of the 4310 admissions to the trauma and acute care surgery service over the twelve month period, 31 (0.7%) patients taking DE were identified. Nine of the 1259 admissions with CT evidence of TBI were taking DE. Three of the 31 patients on DE were excluded because no significant surgical pathology was present. Of the remaining 28, the average age (SD) was 77.14 (10.5), median admission INR/PTT was 1.45/50.3, 11 were on concurrent anti-platelet medications. 6 received DE directed dialysis and 6 received factor Ⅶa. Mortality was 21% (6/28). Results for the subgroups of patients with TBI, injury without TBI, and acute care surgery are displayed in Table 1.

The individual data for the nine TBI injured patients on DE are listed in Table 2. Eight patients (89%) were taking DE for stroke prophylaxis and one for treatment of a prior pulmonary embolism. Recorded dosage was 150mg BID for all 9 subjects. Eight of nine patients had an elevated INR (mean = 1.68) and PTT (mean = 54). Four patients were taking antiplatelet medications concomitantly. Types of intracranial hemorrhage observed in these patients were sub-arachnoid (4), sub-dural (2), combined (2), and intraparenchymal (1). Two of the three patients who received no intervention died: one presented with a non-survivable injury and the second initially appeared to have a minor injury that within hours progressed clinically and radiographically (Figure 1).

DISCUSSION

Coagulopathy and associated bleeding remain significant issues in the trauma population. Coagulopathy due to blood loss is addressed by controlling the ongoing bleed-

Table 2 Data of patients with traumatic brain injury

Case	Age, yr	LOS	iLOS	INR	PTT	Anti-Platelet	CrCl	HD	Ⅶa	FFP	Anti-Platelet	Mortality
1	94	4	3	1.6	61.3	Y	24.1	N	N	Y	Y	N
2	83	1	1	2.5	69	Y	45.6	N	N	N	N	Y
3	79	2	0	1.6	54.3	N	49.8	N	N	N	N	N
4	89	6	3	1.4	35.7	N	40.2	N	N	Y	N	N
5	86	35	5	1.8	50.7	Y	32.4	Y	Y	Y	Y	N
6	64	3	2	1.7	57	Y	99	N	N	Y	N	N
7	88	1	1	1.8	61	N	61.3	N	N	N	N	Y
8	86	2	1	0.9	20	N	46	N	N	Y	N	N
9	82	4	2	1.9	82	Y	46.4	Y	Y	Y	Y	N

LOS: Length of stay; iLOS: Intensive care length of stay; PTT: Partial thromboplastin time.

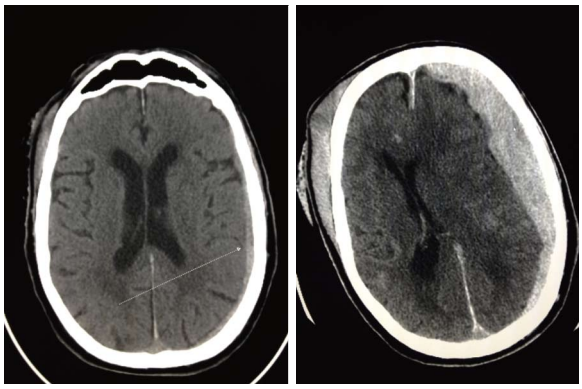

Figure 1 Rapid progression of intracerebral hemorrhage on patient on Dabigatran Etexilate.

ing, keeping the patient warm and perfused, and using accepted protocols to replace blood and blood products. Pharmacologically induced coagulopathy poses a similar risk and is becoming more prevalent, with approximately 1.5 million Americans taking a vitamin K antagonist daily[8]. Treatment of these patients is fairly straightforward as the effect of vitamin K is easily measured and the deficient clotting factors can be replaced.

With the introduction of DE, and subsequent FDA approval of direct factor Xa inhibitors rivaroxaban (Xarelto®) and apixaban (Eliquis®), the trauma surgeon faces a unique challenge in patients with ongoing bleeding who may or may not require surgery. DE is an orally available direct thrombin inhibitor that is rapidly converted to dabigatran and binds to free and clot bound thrombin. Time to maximum concentration is 2 h, half-life is 12-17 h, limited protein binding suggest DE may be dialyzed, and over 80% of the drug is excreted by the kidneys[3,7,9]. The FDA-approved indication is to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation[10].

Advantages of DE include the significant risk reduction of stroke and systemic embolization, predictable pharmacokinetics requiring no coagulation monitoring, a fast onset and offset of action, a relatively short half-life, and limited drug-drug interaction[3,7,11]. Drug cost compared to monitoring with warfarin is revenue neutral. Worldwide there have been at least 260 episodes of post-marketing bleeds resulting in death in patients on DE[12,13]. Our study documents the institutional complication rates of patients on DE and not the effectiveness of DE *vs* oral vitamin K antagonist. The dilemma facing the trauma surgeon is that there is no accepted laboratory test to measure the effect of DE nor are there recommended reversal agents[3,6,7,14]. Both of these factors are especially relevant in the patient with a TBI. The anticoagulant effects have attempted to be quantified in normal human subjects, laboratory animals, and *in vitro* by adding DE to human serum. Assays evaluated include PT, aPTT, factors Ⅱ, Ⅷ, Ⅸ, Ⅹ, and Ⅺ, quantitative D-dimer, reptilase time, von Willebrand factor antigen , antithrombin, plasminogen, thrombin clotting time, protein C activity, ecarin clotting time, and activated protein C resistance[1,11]. Although analytes may be elevated with various concentrations of DE, most notably the aPTT and thrombin clotting time, reported levels frequently are factitiously elevated or low, display incomplete correction, do not correlate with serum levels leading to misdiagnosis and mismanagement, or are insensitive or oversensitive, making virtually any result unreliable[11]. The best determinate of DE effect is knowing the timing of administration, as peak effect is usually two hours after ingestion, the dosage and the patient's renal function (CrCl > 50 provides normal excretion)[9].

Treatment can be simplistic and futile as no known DE counteracting agent exists, so any form of intervention in patients with life-threatening bleeding is empirical. What makes this even more frustrating is the individual trauma surgeon most likely treats a patient taking DE once every several months, has no recommended guidelines, and may be unfamiliar with the intricacies and pharmacokinetics of the most recently approved oral anticoagulant. Considering that not intervening when a patient is actively bleeding is difficult for the treating surgeon, we will discuss the rationale behind several available treatment strategies although all lack even level 3 evidence.

Excluding direct compression, topical thrombin, and simple surgical procedures to obtain hemostasis, viable options to treat extensively injured, TBI, and complex surgical patients taking DE include oral charcoal, activated prothrombin complex concentrates (aPCC), recombinant factor Ⅶa, concentrates of coagulation factors Ⅱ,

IX, and X, and dialysis.

Oral charcoal can be used within two hours of ingestion as charcoal significantly inhibits absorption of DE[6,7]. Kcentra (CSL Behring LLC) is the only four factor prothrombin complex concentrate available in the United States, has not been shown to correct the aPTT in healthy volunteers taking DE, but high doses have been shown to limit intracranial bleeding in rats[3,14]. In a patient with life-threatening bleeding with limited therapeutic options, an INR based dose of 25-50 IU/kg may be justified[6]. Recombinant VIIa has not demonstrated any alteration in the coagulation profile or outcomes in healthy volunteers or laboratory animals taking DE and has documented higher arterial thromboembolic events[15]. Subsequently, salvage therapy with rVIIa should be used cautiously, although a case report suggests high dose therapy (7.2 mg × 2) may be beneficial[16]. Activated PCC has been shown to correct the anticoagulant effect of DE in animal models and reduces clot initiation time in humans *in vitro*. Siegal suggests using aPCC (80 U/kg) over PCC in patients taking DE, but reverses the recommendation for patients taking rivaroxaban (XareltoR) or apixaban (Eliquis), acknowledging that any such recommendation is based on limited data[17]. Kcentra has been shown to partially reverse the effects of factor Xa inhibitors[14].

Dialysis is an attractive option as DE is not plasma bound and excreted renally, but this is the most invasive option and use may be limited due to injury severity. In patients with end-stage renal disease, dialysis removed 62% of circulating DE within two hours, although due to the volume of distribution serum levels rebounded quickly upon cessation of dialysis[9]. Selective case reports suggest that prolonged dialysis (6 h) with flow rates of 700 mL/min improve outcome[16].

Maintaining adequate diuresis is important for all patients, but should not be overlooked as DE is excreted renally. Currently no role exists for desmopressin, protamine sulfate, tranexamic acid, or vitamin K, or fresh frozen plasma[3,6,7]. Platelet concentrates should only be used in cases with thrombocytopenia or concurrent antiplatelet therapies. Although not yet available, a monoclonal antibody directed against DE is under development[17].

In our experience, less than one percent of trauma and acute surgical admissions were taking DE and each surgeon averaged fewer than two patients per year. The percentage of patients with TBI is remarkably similar. With such limited numbers, and reviewing the largest industry sponsored trial (18113 patients) reporting outcomes of 22 patients with TBI, level 1 management recommendations are unlikely[18].

Subsequently, we developed an in-house protocol for patients admitted taking DE, where we obtain baseline clotting studies, a stat hematology consult for major or life-threatening hemorrhage, a nephrology consult for initiation of hemodialysis, and the option of giving a 40 mcg/kg IV dose of rfactor VIIa or Kcentra.

Our study is limited by the small sample size and retrospective collection of the data. Additionally, recommendations extrapolated from the literature combine data from multiple laboratories and include human, animal, and *in-vitro* studies. Finally, treatment is individualized and up to the discretion of the surgeon.

In a conclusion, DE is a cost-neutral highly effective oral direct thrombin inhibitor approved recently along with two factor Xa inhibitors, rivaroxaban and apixaban. Management of the traumatic brain injury patient taking DE poses unique and confounding issues as the effect of DE is not measurable and no reversal agents are currently recommended. Trauma surgeons manage patients on DE infrequently and such encounters may be frustrating. For patients taking DE, strategies for non-operative management of bleeding are discretionary and institution dependent and include oral charcoal, maintaining adequate diuresis, PCC, aPCC, and dialysis.

COMMENTS

Background

Seventy million Americans will be over the age of 65 by 2030 and five percent of these patients have atrial fibrillation and are candidates for anticoagulation. In 2010, the ACC Foundation and the AHA added Dabigatran Etexilate (DE) to their treatment guidelines with a class 1 recommendation for non-valvular atrial fibrillation. DE is an attractive alternative to warfarin (WF) due to improved outcomes and the lack of need for serial monitoring. However, it poses a risk to the trauma population because of an extended half-life and the lack of a reversal agent. Therefore it was our aim to review the outcomes of patients with TBI on DE.

Research frontiers

DE and other novel anticoagulants that lack a true reversal agent post a unique dilemma for trauma surgeons. Local care plans should be initiated until dose specific reversal agents are commercial available.

Applications

Current practice guidelines should be available to aid in managing patients with traumatic brain injury on DE. Therapeutic options include: oral charcoal, maintaining adequate diuresis, prothrombin complex concentrates, activated prothrombin complex concentrates, and dialysis.

Terminology

Dabigatran Etexilate is a new oral anticoagulant that works by directly inhibiting thrombin in the clotting cascade.

Peer review

This is a single institution observation study and it is limited as such. Future research goals will be multi institution collaborations on not just DE but other novel agents in the hopes of developing nationwide guidelines for treatment of novel agents until industry specific antidotes are commercially available.

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CASE REPORT

Desmoplastic small round cell tumor with atypical immunohistochemical profile and rhabdoid-like differentiation

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Abstract

Desmoplastic small round cell tumor (DSRCT) is a rare, aggressive malignant neoplasm of unknown origin, and is comprised of small round cells with a characteristic desmoplastic stroma. DSRCT typically expresses epithelial, mesenchymal and neural markers simultaneously. We describe a case of DSRCT with an atypical immunohistochemical profile and rhabdoid-like tumor cells on electron microscopy. In the present case, the neoplastic cells were positive only for vimentin, desmin (cytoplasmic membranous pattern) and CD56, and negative for smooth muscle actin, synaptophysin, CD117, CD45, myogenin, CAM5.2, pancytokeratin, WT1, EMA, CD99, neurofilament, CD34 and p53. Ki67 showed a low proliferative activity. Electron microscopy showed focal rhabdoid differentiation. However, INI-1 (SNF-5/BAF47) demonstrated preservation of nuclear positivity in the neoplastic cells. Cytogenetic studies showed translocation t(11;22)(p13;q12) confirming an EWSR1-WT1 translocation characteristic for DSRCT, and t(1;15)(q11;p11.2) of unknown significance. This case is a diagnostic challenge because of atypical immunohistochemical profile and cytogenetic study is crucial in rendering the correct diagnosis.

Key words: Desmoplastic small round cell tumor; Ultrastructure; Cytogenetics; Rhabdoid cells; EWSR1-WT1

Core tip: We describe a case of desmoplastic small round cell tumor (DSRCT) with an atypical immunohistochemical profile and rhabdoid-like tumor cells on electron microscopy (EM). DSRCT typically expresses epithelial, mesenchymal and neural markers simultaneously. In this case, the neoplastic cells were positive only for vimentin, desmin and CD56 and negative for epithelial and other muscle markers. EM showed focal rhabdoid differentiation, but INI-1 (SNF-5/BAF47) demonstrated preservation of nuclear positivity in the neoplastic cells. Cytogenetic studies showed translocation t(11;22)(p13;q12) confirming an EWSR1-WT1 translocation characteristic for DSRCT, and t(1;15)(q11;p11.2) of unknown significance.

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INTRODUCTION

Desmoplastic small round cell tumor (DSRCT) was first

described in 1989[1,2]. DSRCT is a rare, aggressive malignant neoplasm of unknown origin, and is comprised of small round cells with a characteristic desmoplastic stroma. DSRCT is most common in children and young adults (mean age 22 years), with a male predominance (male to female ratio 4:1)[3]. The most common location is the abdominal and/or pelvic cavity, but it has been described in many organ systems, including ovary, paratesticular region, kidney, lung, pleura, parotid gland and central nervous system[4-11]. Typically, DSRCT has a distinctive immunohistochemical profile and expresses polyphenotypic markers simultaneously. The tumor cells usually express epithelial (cytokeratin, epithelial membrane antigen), mesenchymal (desmin, vimentin) and neural (neuron-specific enolase, chromogranin, synaptophysin) markers. Desmin immunoreactive displays in a perinuclear *dot-like* Golgi *pattern*. DSRCTs with atypical morphology or immunohistochemical features have been reported[12,13]. Cytogenetics, FISH, RT-PCR and molecular testing are crucial in rendering the correct diagnosis[14].

DSRCT is associated with a unique chromosomal *translocation* t(11:22)(p13;q12) which involves the Ewing sarcoma gene breakpoint region 1 (*EWSR1*) on 22q13 and the Wilms tumor gene (*WT1*) on chromosome 11p13[15]. *EWSR1* gene encodes EWS protein, which is a multifunctional protein associated with gene expression, cell signaling, and RNA processing and transport. *WT1* is a tumor suppressor gene that encodes a zinc finger protein which regulates several growth factors, including platelet-derived growth factor-A (PDGFA)[16]. The most common breakpoints involve the intron between *EWSR1* exon 7 and 8 and the intron between *WT1* exons 7 and 8, although breakpoint variations have been described[17-19].

CASE REPORT

An 8 years old male with no known significant past medical history presented with 1 wk history of vague abdominal pain. The child was afebrile, had regular bowel movements, tolerated a regular diet, and denied nausea and vomiting. Physical examination showed a mildly distended abdomen without a readily palpable mass. CT of the abdomen and pelvis revealed a 17-cm heterogeneously enhancing complex cystic lesion, which displaced the colon and small intestine laterally and superiorly. On exploratory laparotomy, the mass was adherent to the omentum. The mass was tossed, with large dilated blood vessels on the external surface of the tumor. The patient tolerated the surgical procedure well.

Gross pathology

Upon gross examination, the mass was encapsulated, lobulated and measured 17.0 cm × 11.0 cm × 5.0 cm, with attached omental tissue (Figure 1A, B). Cross sections of the mass showed variegated cut appearance ranging from tan to red to black in color. Focal areas of hemorrhage and necrosis were noted.

Microscopic and immunohistochemical features

Microscopic examination showed small round cell aggregates embedded in a fibromyxoid stroma (Figure 1C-F). The tumor cells were round to oval with scant cytoplasm, hyperchromatic nuclei and inconspicuous nucleoli. However, certain tumor cells have a different histomorphologic appearance with enlarged nuclei, open chromatin and prominent nucleoli. Focal tumor necrosis and hemorrhage were present, corresponding to these features seen upon gross examination. Prominent vascular proliferation was associated with the tumor. An atypical immunophenotype (Figure 2A-D) was demonstrated. The tumor cells were positive only for vimentin, desmin (cytoplasmic membranous pattern) and CD56, while being negative for smooth muscle actin, synaptophysin, CD117, CD45, myogenin, CAM5.2, pancytokeratin, WT1, EMA, CD99, neurofilament, CD34 and p53. Ki67 showed a low proliferative activity.

Ultrastructural features

Electronic microscopy (Figure 2E, F) showed closely apposed tumor cells with rudimentary intercellular junctions and without myofilaments, dense core neurosecretory granules, cytokeratin-like intermediate filaments and no glycogen aggregates. The tumor cells had irregular nuclear outlines, prominent heterochromatin and moderate cytoplasm. There was readily identified rhabdoid differentiation within a certain population of tumor cells. These tumor cells had large aggregates of cytoplasmic filaments that displaced the nuclei to the periphery of the cell, with some tumor cells having indented nuclear profiles. There were also entrapped organelles within cytoplasmic filament whirls. Upon discovery of these rhabdoid cells on ultrastructural examination, immunohistochemical staining for INI-1 (SNF-5/BAF47) was performed. Surprisingly, all tumor cells demonstrated preservation of nuclear positivity, eliminating rhabdoid tumor from the differential diagnosis.

Cytogenetics

Upon cytogenetic analysis, the karyotype of the cultured tumor cells was shown to be 46,XY, t(11;22)(p13;q12)[12]/92, idemx2[4] with t(1;15)(q11;p11.2). The t(11;22) translocation harbored the *EWSR1-WT1* translocation, a tumor-defining feature of DSRCT. A diagnosis of DSRCT with rhabdoid-like cell component was rendered.

DISCUSSION

The differential diagnosis of a "small round cell tumor" includes Ewing sarcoma, Wilms tumor, neuroblastoma, medulloblastoma, rhabdomyosarcoma, small cell osteosarcoma, small cell synovial sarcoma, small cell carcinoma, lymphoma, and rhabdoid tumor. DSRCT has characteristic immunohistochemical features, with expression of epithelial, mesenchymal and neural markers simultaneously, which is helpful in differentiating DSRCT from other "small round cell tumors". However

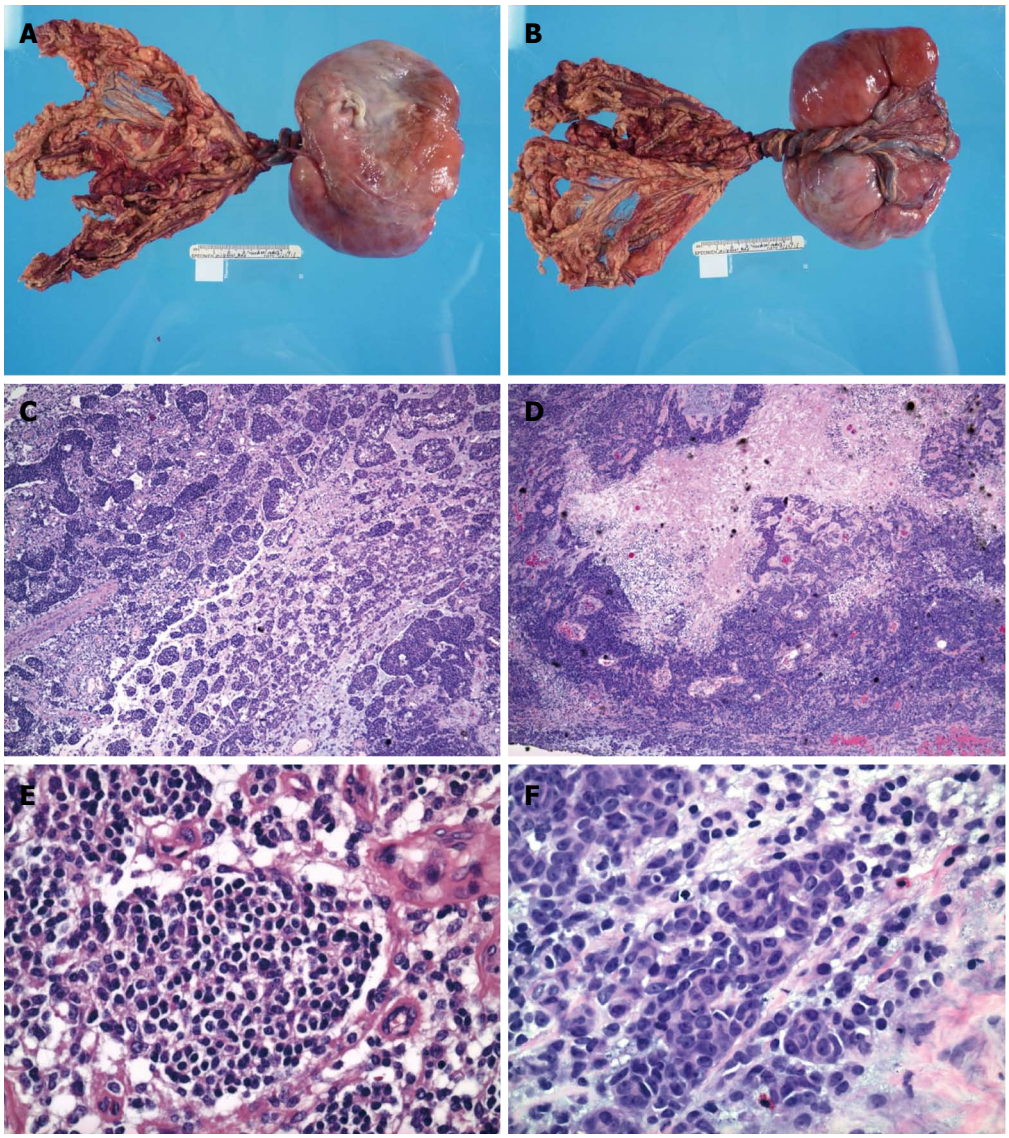

Figure 1 Gross and microscopic feature of abdominal mass. A, B: Gross examination showed an encapsulated and lobulated soft tissue mass with attached omental tissue; C-F: The small round cell tumor possessed round to oval hyperchromatic nuclei with inconspicuous nucleoli and scant cytoplasm. Focal tumor cells with enlarged nuclei, open chromatin and prominent nucleoli, as well as rhabdoid differentiation were noted. Focal tumor necrosis and hemorrhages were present (HE staining).

in the present case, the tumor cells were negative for many epithelial, myogenic and neural markers and positive only for vimentin, CD56 and desmin. CD56 is a nonspecific marker, and expressed in many "small round cell tumors", including alveolar rhabdomyosarcoma, embryonal rhabdomyosarcoma, neuroblastoma, Wilms tumor, neuroendocrine neoplasms and undifferentiated sarcoma[20]. Desmin showed a cytoplasmic membranous pattern, instead of the typical perinuclear dot-like Golgi pattern characteristic for DSRCT. The atypical immunohistochemical features made it difficult to make a correct diagnosis by morphologic and immunohistochemical features alone. DSRCT lacking epithelial markers and/or divergent immunophenotype has been described in several reports[12,13,21]. Cytogenetic and molecular studies are crucial in these cases in rendering an accurate diagnosis.

DSRCT can have many morphologic variations[22-24]. In our case, focal rhabdoid differentiation was identified on EM. However, the nuclear expression of SNF-5(INI1/BAF47) was preserved in the tumor cells, which did not support a diagnosis of rhabdoid tumor. The ultrastructural features of DSRCT include intracellular whirls and packets of intermediate filaments that usually fill the cytoplasm and displace the nucleus, while entrapping cytoplasmic organelles within the filaments[25-27]. Rhabdoid differentiation, as well as focal areas with increased nuclear atypia, has been previously described in DSRCT[28]. Although DSRCT usually has a desmoplastic stroma, this was not present in our case. Prominent vascular proliferation can be seen in DSRCT, as in our case, and the differential diagnosis of infiltrating glomus tumor may be entertained. However, infiltrating glomus tumor typically expresses smooth muscle actin and variably desmin. Other morphologic variations previously described

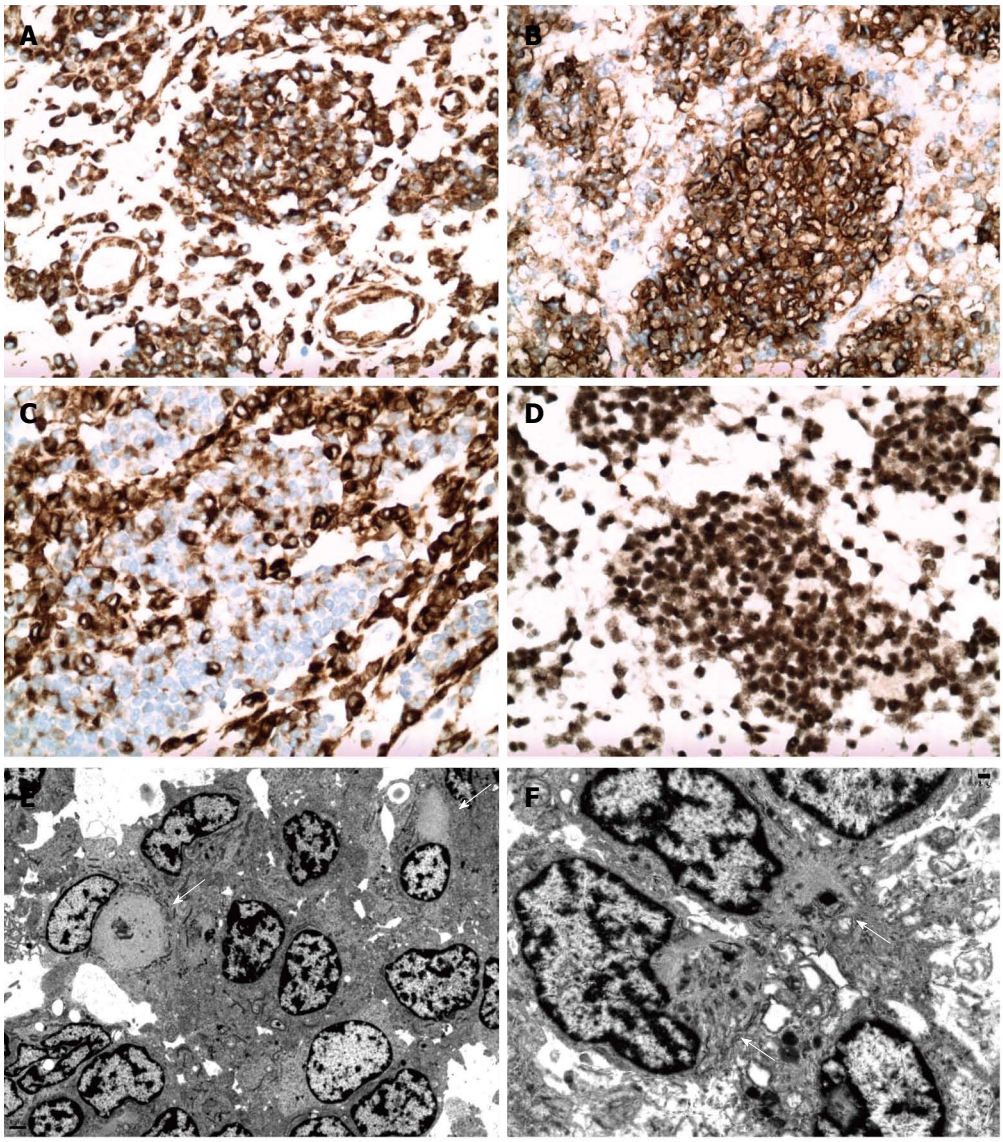

Figure 2 Immunohistochemical and ultrastructural features of abdominal mass. Tumor cells exhibited strong diffuse cytoplasmic vimentin expression (A), diffuse membranous CD56 expression (B), cytoplasmic and membranous desmin expression (C), and nuclear INI-1 reactivity (SNF-5/BAF47) with tumor cells and non-neoplastic cells. Electron microscopy (E, F) showed closely apposed tumor cells with irregular nuclear outlines and heterochromatin. There were intermixed tumor cells with aggregates and whirls of intermediate filaments (arrows) that displaced the nuclei and entrapped organelles.

in DSRCT, such as signet ring-like appearance, "zellballen" pattern, tubular-like structure or papillary areas were not identified in our case[23,29].

Interestingly, our case not only had an unusual immunohistochemical profile, but also a unique karyotype. Cytogenetic study showed translocation t(11;22)(p13;q12), which is characteristic of DSRCT, and an additional translocation t(1;15)(q11;p11.2). Even though the characteristic *EWSR1/WT1* translocation can be detected by reverse transcription polymerase chain reaction (RT-PCR), cytogenetic testing is necessary to detect tumor-defining translocations, novel translocations and complex karyotypic aberrations. Of note, the INI-1 (hSNF5) gene is located at 22q11.2 in close proximity to EWSR1. This close proximity may have led to dysregulation of the IN1-1 gene function without loss of INI-1 gene protein expression. Rhabdoid tumors without INI-1 gene loss or mutation and expression of INI-1 gene protein have been reported[30]. These rhabdoid tumors have loss or mutation of *SMARCA4* (19p13.2) which dysregulates a signaling pathway downstream from INI-1 gene protein function. In an extensive search of the English language literature, the t(1;15)(q11;p11.2) has not been previously reported in pediatric neoplasia. Of interest, translocations involving 1q11 have been reported in myelodysplastic syndromes. The pericentromeric region of chromosome 1 is an unstable region involved in several chromosomal rearrangements. A possibility is that the heterochromatin of chromosome 1 may have a silencing effect, or otherwise interfering effect, with genes present in the region involved in the translocation. Few myelodysplastic syndrome cases with a der(1;15) translocation have been reported[31].

In the present case, infrequent tumor cells also showed

tetraploid clonal evolution, which is common in many tumors and has been previous reported in DSRCT[32]. Our hypothesis is that the unusual immunohistochemical profile in our case was due to the complex karyotype. It is debatable if the tumors with complex karyotype should still be called DSRCT or a new category of "gray zone small blue cell tumor" should be created in the future. Currently, no standard oncologic therapy is available for DSRCT and the prognosis is dismal even with multimodality oncologic therapy[33-35]. The 5-year survival rate is approximately 15%[35]. The prognosis significance of DSRCT with complex karyotype is currently unclear.

COMMENTS

Case characteristics

An 8 years old male with no known significant past medical history presented with 1 wk history of vague abdominal pain.

Clinical diagnosis

The child was afebrile, had regular bowel movements, tolerated a regular diet, and denied nausea and vomiting. Physical examination showed a mildly distended abdomen without a readily palpable mass.

Differential diagnosis

Electronic computer X-ray tomography technique of the abdomen and pelvis revealed a 17-cm heterogeneously enhancing complex cystic lesion, which displaced the colon and small intestine laterally and superiorly.

Treatment

The authors describe a case of desmoplastic small round cell tumor with an atypical immunohistochemical profile and rhabdoid-like tumor cells on electron microscopy.

Experiences and lessons

This case is a diagnostic challenge because of atypical immunohistochemical profile and cytogenetic study is crucial in rendering the correct diagnosis.

Peer review

The authors report an atypical small round cell tumor case. The manuscript is clearly written and the case is of interest.

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CASE REPORT

Resolution of hemolysis from pump thrombus during left ventricular assist device exchange

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Author contributions: All of the authors contributed in drafting the article, critical revision and writing the manuscript; Unai S and Hirose H collected the patient's clinical data; all the authors approved the final version of the manuscript.

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Abstract

A 50-year-old male who underwent a HeartMate Ⅱ left ventricular assist device placement for ischemic cardiomyopathy presented with discolored urine and hemolysis 3 mo after the operation. His hemolysis was thought to be due to thrombosis within the pump. Imaging studies were not able to visualize a left ventricular thrombus. Medical management with anticoagulation failed and he underwent surgery for a pump exchange. Intraoperatively, a firm thrombus was found within the pump of the HeartMate Ⅱ, and the color of the urine changed dramatically from cola-colored to yellow which enabled us to confirm the diagnosis.

Key words: Cardiac surgery; Hemolysis; Left ventricular assist device; Thrombosis

Core tip: Diagnosis of pump thrombosis is difficult, but the intraoperative change of the color of urine may be seen almost immediately after pump exchange. This report also highlights the technical aspect of replacing the HeartMate Ⅱ pump, and we believe the images are educational for the readers.

Unai S, Hirose H, Entwistle JWC, Samuels LE. Resolution of hemolysis from pump thrombus during left ventricular assist device exchange. *World J Clin Cases* 2014; 2(8): 373-376 Available from: URL: http://www.wjgnet.com/2307-8960/full/v2/i8/373.htm DOI: http://dx.doi.org/10.12998/wjcc.v2.i8.373

INTRODUCTION

HeartMate Ⅱ (Thoratec, Pleasanton, CA) is a continuous flow left ventricular assist device (LVAD), which has improved the quality of life and survival of patients who have end-stage heart failure refractory to medical therapy. The device is consisted of an inflow cannula in the left ventricle, axial flow pump, and an outflow graft to the ascending aorta. It is designed for long-term usage, either bridge to transplant or destination therapy. Since 2006, more than 10000 HeartMate Ⅱ LVADs have been implanted, and 2500 LVADs have been implanted in 2013, according to the INTERMACS registry[1]. Consequently, the incidence of device-related complications, such as pump thrombosis, infection, bleeding, has increased, which often require re-admission and/or surgery[2]. Pump thrombosis is one of the common causes of hemolysis in patients with LVAD. Hemolysis related to the LVAD could be due to kinking of the outflow graft, malposition of the inflow cannula, or malfunction of the pump. We present a case of an LVAD thrombosis that presented with hemolysis and discolored urine 3 mo after the LVAD placement. The patient failed conservative medical management and underwent surgery for pump exchange. Thrombus was seen in the pump and the color of the urine changed dramatically after the pump was exchanged which enabled us to confirm the diagnosis of pump thrombosis.

CASE REPORT

A 50-year-old male with a history of axillo-bifemoral

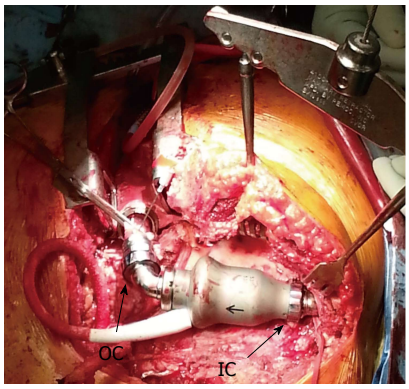

Figure 1 Intraoperative photo after the replacement of the pump. IC: Inflow connection; OC: Outflow connection.

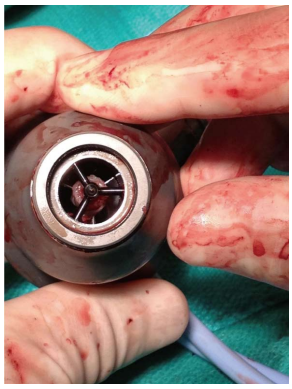

Figure 2 Inspection of the pump revealed a firm thrombus along the inlet stator.

bypass for bilateral chronic iliac artery occlusive disease, ischemic cardiomyopathy with an ejection fraction of 20%, underwent placement of a HeartMate Ⅱ LVAD as a bridge to cardiac transplantation. Preoperative hematology work-up disclosed no evidence of hypercoagulability. Heparin infusion was started on postoperative day 1 and warfarin was started on postoperative day 3. Heparin drip was maintained with a goal PTT level of 60 to 70 s until the INR reached 1.8. He was discharged on postoperative day 15 on aspirin 325 mg and warfarin with a target INR of 1.8 to 2.5. Upon discharge, the LVAD was set at 9200 rpm, giving a flow of 5.7 L/min, with a pulsatility index (the pulsatility of the flow through the pump) of 5.5 and pump power (a direct measurement of motor voltage and current) of 6.7 watts.

Three months later on his scheduled office visit, his lactate dehydrogenase (LDH) was found to be elevated to 1352 IU/L (Table 1). His baseline LDH level was between 400 and 500 IU/L. Interrogation of the pump parameters revealed several episodes of elevation in the pump power a few days before the office visit that had since resolved. It was thought to be due to a small pump thrombus that resolved spontaneously. Ten days later, he was admitted to the hospital due to discolored urine. Urine analysis showed strongly positive hemoglobin, very few red blood cells, and white blood cells. He denied any chest pain, shortness of breath, or edema. There were no signs of infection. Hemoglobin was 7.6 g/dL, plasma free hemoglobin was 52.0 mg/dL. The LDH, haptoglobin, AST were unable to be measured due to severe hemolysis. Other lab values included INR 1.7, serum creatinine 1.9 mg/dL (baseline 1.2 mg/dL), total bilirubin 1.1 mg/dL. Echocardiography showed severe biventricular dysfunction and opening of the aortic valve with every heartbeat. The velocity through the inflow cannula was 1.1 m/s. The LVAD parameters showed occasional pump power elevation over 9 watts. Heparin was initiated but there was no resolution of the discolored urine over three days. Although echocardiography and chest CT scan failed to demonstrate a thrombus, he was clinically diagnosed with pump thrombosis. Due to the persistently elevated creatinine and requirement of multiple blood transfusions for hemolytic anemia despite optimum medical therapy, the decision was made to proceed with pump exchange.

After resternotomy, cardiopulmonary bypass (CPB) was established with ascending aorta and right femoral vein cannulation, as the femoral arteries were not able to be cannulated due to iliac artery occlusions. To gain access to the inflow portion of the LVAD, a left subcostal incision was added and the body of the HeartMate Ⅱ pump was removed by unscrewing the inflow- and outflow- connections. It was replaced with a new HeartMate Ⅱ pump (Figure 1). There was no thrombus in the inflow cannula or outflow conduit. Intraoperative inspection of the original LVAD interior demonstrated a firm thrombus along the inlet stator (Figure 2). The urine color was tea-colored before CPB (Figure 3A). It changed to reddish upon cessation of flow from the original LVAD and institution of CPB (Figure 3B). Following initiation of the new LVAD flow and discontinuation of CPB, it changed to a yellow color (Figure 3C). Postoperative recovery was steady and his renal function recovered with clear urine (Table 1). Anticoagulation therapy consisted of intravenous heparin with overlapping warfarin (INR 2.5 to 3.5), aspirin 325 mg, and clopidogrel 75 mg. He was discharged home on postoperative day 8. The patient was symptom free afterwards, and underwent heart transplant 2 mo later.

DISCUSSION

LVAD therapy requires a balance between anticoagulation and hemostasis to prevent the complications of bleeding and thrombosis. There are many anticoagulation regimens to achieve this goal, and most combine inhibition of the clotting cascade with warfarin and at least one antiplatelet agent. The optimal anticoagulation/antiplatelet strategy remains elusive because of the heterogeneity in the reaction between the biological components (*i.e.*, blood) and artificial surfaces (*i.e.*, LVAD) as well as the variability in the responsiveness to anticoagulants and anti-platelet medications[3]. As a result of this imperfect coexistence between "man" and "machine", the lead-

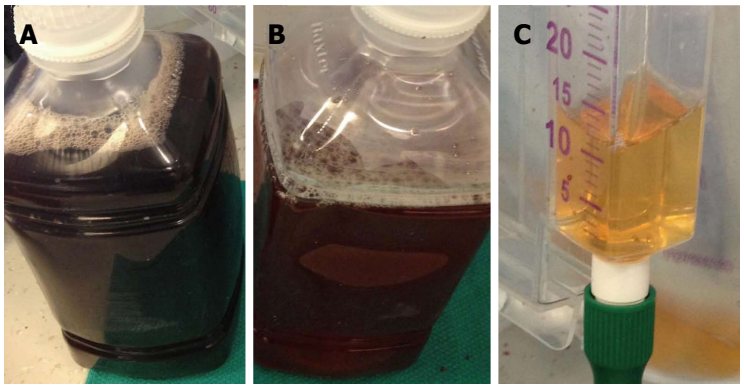

Figure 3 Urine color. A: Before CPB; B: After CPB and cessation of the old pump; C: After pump replacement. CPB: Cardiopulmonary bypass.

Table 1 Laboratory values

	Outpatient (1 mo prior to admission)	Outpatient (1 wk prior to admission)	Admission	Post pump exchange (POD 7)
White blood cells (B/L)	6.5	6.7	8	10.7
Hemoglobin (g/dL)	10.8	8.4	7.6	11.6
Hematocrit	35.1%	27.9%	24.5%	36.4%
Platelets (B/L)	158	139	164	162
Reticulocytes			7.4%	2.8%
Na (mEq/L)	139	136	131	137
K (mEq/L)	4	4.7	4.9	3.8
BUN (mg/dL)	17	16	28	26
Creatinine (mg/dL)	1.2	1.4	1.9	1.5
Total bilirubin (mg/dL)	0.4	0.5	1.1	0.9
Aspartate aminotransferase (IU/L)	40	60	[1]	34
Lactate dehydrogenase (IU/L)	707	1382	[1]	527
Plasma free hemoglobin (mg/dL)			52	6.4
Haptoglobin (mg/dL)			[1]	
Urine color			Light red	Yellow
Red blood cell in urine (/HPF)			1	< 1

[1]Unable to be obtained due to hemolysis.

ing causes of LVAD readmissions include bleeding and thrombosis. Thrombosis of the LVAD is a potentially lethal complication which occurs in 2% to 3% of the patients who receive the HeartMate Ⅱ LVAD and the incidence is reported to be increasing[4-6]. Patients typically present with elevated pump power, heat over the pump, heart failure and signs of hemolysis. Echocardiography may show opening of the aortic valve due to inadequate decompression of the left ventricle (LV) and increased LV end-diastolic diameter. Serial recording of LV end-diastolic diameter while increasing the pump speeds may diagnose pump thrombus or other flow obstructions[7]. However, there have been reports of pump thrombosis with normal echo and pump parameters as well[8,9]. Hemolysis may be the only sign of thrombosis, although hemolysis may be due to various reasons, such as kinking of the outflow graft, malposition of the inflow cannula or the pump itself (high shear stress, *etc.*)[8,9]. The diagnostic challenge is that pump thrombus may not be visualized with contrast CT scan or echocardiography, due to artifacts caused by the metallic housing of the LVAD[8]. In our case, we were able to confirm that the hemolysis was due to pump thrombosis by intraoperative inspection of the removed pump and the resolution of the urine after pump exchange.

Change of urine color is easily noticeable to patients and should be promptly addressed as a sign of possible pump thrombosis. In the current era of non-pulsatile LVAD therapy, it is likely that the risk of pump thrombosis and hemolysis will remain, and LVAD exchange may be necessary in cases that are refractory to medical management. Fortunately, the modular nature of LVAD technology allows for pump exchange with a reasonable degree of safety; the mortality is reported to be 6% to 7%[10,11]. In contrast, medical management; adding anti-platelet agents such as dipyridamole or clopidogrel, increasing the dose of aspirin and/or increasing the target PT-INR for anticoagulation, resulted in a 48.2% mortality in the following six months after the diagnosis of pump thrombosis[6].

In conclusion, thrombosis during LVAD therapy is a potentially life-threatening complication requiring prompt diagnosis and management. We presented a report of LVAD thrombosis causing hemolysis and discoloration of the urine that resolved promptly after the pump exchange. The diagnosis is challenging, but we were able to confirm the diagnosis by intraoperative inspection of the pump and the prompt resolution of the discolored urine.

COMMENTS

Case characteristics

A 50-year-old-male with a history of HeartMate II implantation presented with

discolored urine.

Clinical diagnosis

He denied any chest pain, shortness of breath, or edema.

Differential diagnosis

Discolored urine and the lab values suggesting hemolysis, occasional pump power spikes were thought to be due to pump thrombosis.

Laboratory diagnosis

Hemoglobin 7.6 g/dL; plasma free hemoglobin 52.0 mg/dL; PT-INR 1.7; serum creatinine 1.9 mg/dL; total bilirubin 1.1 mg/dL. The lactate dehydrogenase, haptoglobin, AST were not able to be measured due to severe hemolysis.

Imaging diagnosis

Echocardiography showed severe biventricular dysfunction and opening of the aortic valve with every heartbeat.

Treatment

The patient underwent pump exchange.

Related reports

Medical management resulted in a 48.2% mortality in the following six months after the diagnosis of pump thrombosis.

Experiences and lessons

The diagnosis of pump thrombosis is challenging, but the authors were able to confirm the diagnosis by intraoperative inspection of the pump and the prompt resolution of the discolored urine.

Peer review

The manuscript describes frequent complication of left ventricular assist device. The manuscript is well written and has a good structure with excellent images.

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CASE REPORT

Transthoracic echo: A sensitive tool for detecting cardiac extension of renal cell carcinoma?

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Author contributions: Bejarano M and Cameron YL designed the report; Movahed A and Bejarano M were attending physicians for the patient; Koutlas TC performed the surgical operation; Bejarano M and Movahed A performed the image diagnosis.

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Abstract

Renal cell carcinoma is a common urological malignancy with the unique ability to invade the inferior vena cava (IVC) and to extend into the right atrium of the heart. Of those with Renal cell carcinoma only 4%-25% are found to have IVC invasion and of those only 2%-10% extend into the right atrium. If treated surgically, extension of tumor thrombus is not a determinant of survival; therefore it is imperative to determine the presence and extent of tumor thrombus in order to determine surgical approach and tumor resection. To date this has been primarily accomplished by magnetic resonance imaging and computed tomography. We present a case of 61 years old African American woman in which transthoracic echocardiography provided a more accurate determination/characterization of the presence and degree of tumor thrombus and extension.

Key words: Renal cell carcinoma; Tumor thrombus; Cardiac extension; Right atrial mass

Core tip: Renal cell carcinoma is a common urological malignancy with the ability to invade the inferior vena cava and to extend into the right atrium of the heart. If treated surgically, extension of tumor thrombus is not a determinant of survival; therefore it is imperative to determine the presence and extent of tumor thrombus. To date, this has been primarily accomplished by magnetic resonance imaging and computed tomography; however, we present a case in which transthoracic echocardiography provided a more accurate determination/characterization of the presence and degree of tumor thrombus and extension.

Bejarano M, Cameron YL, Koutlas TC, Movahed A. Transthoracic echo: A sensitive tool for detecting cardiac extension of renal cell carcinoma? *World J Clin Cases* 2014; 2(8): 377-379 Available from: URL: http://www.wjgnet.com/2307-8960/full/v2/i8/377.htm DOI: http://dx.doi.org/10.12998/wjcc.v2.i8.377

INTRODUCTION

Renal cell carcinoma is a common urological malignancy with the unique ability to invade the inferior vena cava (IVC) and to extend into the right atrium of the heart. Of those with Renal cell carcinoma (RCC) only 4%-25% are found to have IVC invasion and of those only 2%-10% extend into the right atrium. If treated surgically, extension of tumor thrombus is not a determinant of survival; therefore it is imperative to determine the presence and extent of tumor thrombus in order to determine surgical approach and tumor resection. To date this has been primarily accomplished by magnetic resonance imaging (MRI) and computed tomography (CT).

CASE REPORT

A 61 years old African-American female with past medi-

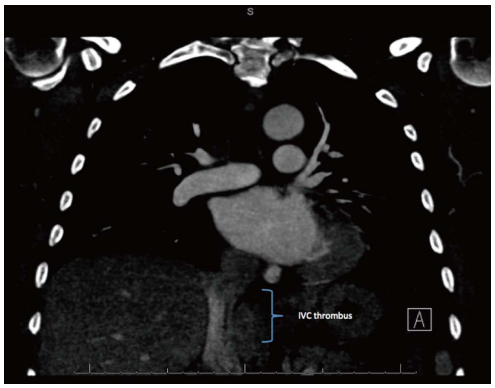

Figure 1 Computed tomography scan (coronal view) revealing inferior vena cava thrombus with no evidence of extension into the right atrium.

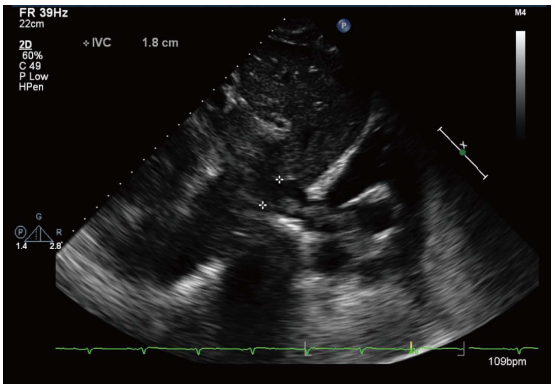

Figure 3 Subcostal view showing the tumor thrombus extending from the inferior vena cava into the right atrium.

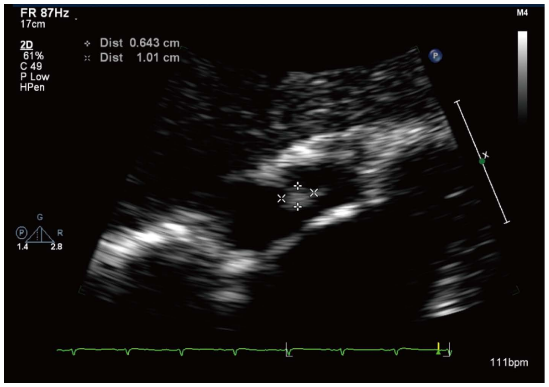

Figure 2 Subcostal view showing the right atrial thrombus.

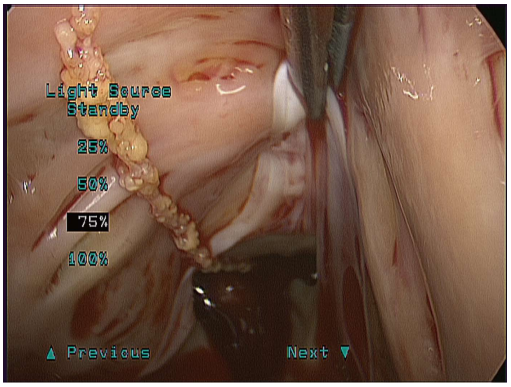

Figure 4 Peri-operative view of the tumor thrombus within the inferior vena cava extending into the right atrium.

cal history of hypertension, hyperlipidemia, and diabetes mellitus initially presented to her primary care physician for progressively worsening fatigue, anorexia, and weight loss. As part of her work-up, she underwent an abdominal and pelvis CT scan, which revealed a large right sided renal mass with possible invasion of the right renal vein and inferior vena cava. A follow up abdominal MRI confirmed the presence of a very large right-sided renal mass consistent with renal cell carcinoma and subsequent invasion of the right renal vein and adjacent inferior vena cava. Further assessment revealed a tumor thrombus extending beyond the renal veins into the intrahepatic inferior vena cava and toward the right atrium. In order to fully characterize the extent of tumor thrombus extension, a CT angiogram (CTA) of the chest and transthoracic echocardiogram (TTE) was done. The chest CTA revealed a filling defect in the IVC in the intrahepatic and subhepatic regions consistent with known tumor thrombus, but showed no evidence of right atrium invasion (Figure 1). On the other hand, the TTE showed a large right atrial mass (Figure 2) with diastolic prolapse into the right ventricle and extension into the IVC (Figure 3). In the setting of her known history of RCC with migration and the fact that this mass was also seen to extend into the IVC, it was felt that this was indeed right atrial invasion of the tumor thrombus and less likely to be a hematological thrombus. A preoperative left heart catheterization was also performed revealing significant mid right coronary artery disease.

After completing the aforementioned preoperative assessment and evaluation by Urology, Vascular Surgery and Cardiothoracic Surgery, the patient underwent a radical nephrectomy and resection of the inferior vena cava and right atrial tumor thrombi (Figure 4). She simultaneously underwent a single vessel coronary artery bypass for her right coronary artery disease. There were no surgical complications and the patient's postoperative course was unremarkable.

DISCUSSION

Renal cell carcinoma tumor thrombus has a propensity to invade the main renal veins as well as the IVC and in rare circumstances can extend into the right atrium of the heart[1,2]. In order to properly classify RCC extension and plan the appropriate surgical technique and approach, one would imagine that establishing the location of the superior margin of the tumor thrombus would be essential[1,3]. At this time the mainstay or gold standard of renal mass detection and characterization (including RCC) is CT scan and MRI[1,4,5]. CT scan has shown to be

Table 1 Classification of renal cell carcinoma tumor thrombus

Tumor thrombus level[6]	Characteristics[6]
Level Ⅰ	Extension to 2 cm above the renal vein into the IVC
Level Ⅱ	Extension to the subhepatic level, > 2 cm above the renal vein BUT below the diaphragm
Level Ⅲ	Extension into the intrahepatic IVC BUT below the diaphragm
Level Ⅳ	Extension into the right atrium of the heart

IVC: Inferior vena cava.

most accurate in evaluating the extent of local growth as well as the presence or absence of metastasis (*i.e.*, to the pancreas, bone). On the other hand MRI has been more accurate in delineating the superior margin of any tumor thrombus, and thereby classifying RCC tumor thrombus, as well as differentiating between bland/hematologic thrombus and tumor thrombus[1,4,5]. Traditionally TTE has been used to further delineate the supradiaphragmatic extension of tumor thrombus. In our case, TTE accurately illustrated the cranial extent of tumor thrombus into the right atrium which was in fact missed on the traditionally used CT scan.

For level IV tumors (Table 1) such as was found in our patient, cardiopulmonary bypass (CPB) with or without hypothermic circulatory arrest (HCA) is necessary for safe and complete extraction of the thrombus[1,3,6]. This surgical approach provides a bloodless surgical field that allows optimal visualization of the hepatic veins, IVC and Right Atrium for complete tumor thrombus resection. As incomplete resection of these tumors confers a higher rate of metastatic recurrence and decreased postoperative survival, it is imperative to clearly delineate the superior margin of any tumor thrombus[1,3,6].

In our case, the patient's preoperative evaluation included a CT abdomen/pelvis, CT chest, MRI abdomen, and TTE. Unexpectedly, it was the TTE that provided the most accurate determination of the cranial extent of the tumor thrombus. Proper classification of the tumor thrombus allowed for the appropriate surgical approach to be undertaken ensuring the best patient outcome.

COMMENTS

Case characteristics

A 61 years old African-American female with past medical history of hypertension, hyperlipidemia, and diabetes mellitus initially presented to her primary care physician for progressively worsening fatigue, anorexia, and weight loss.

Clinical diagnosis

A large right sided renal mass with possible invasion of the right renal vein and inferior vena cava.

Imaging diagnosis

Chest computed tomography angiogram revealed a filling defect in the inferior vena cava (IVC) in the intrahepatic and subhepatic regions consistent with known tumor thrombus, the transthoracic echocardiogram (TTE) showed a large right atrial mass with diastolic prolapse into the right ventricle and extension into the IVC.

Experiences and lessons

In this case, TTE accurately illustrated the cranial extent of tumor thrombus into the right atrium which was in fact missed on the traditionally used computed tomography scan.

Peer review

The case report illustrates the diagnostic power of transthoracic echo in diagnosis of cardiac extension of renal cell carcinoma. The manuscript is well written.

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CASE REPORT

Prucalopride-associated acute tubular necrosis

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Abstract

We report the first case of acute renal failure secondary to prucalopride, a novel agent for the treatment of chronic constipation. The 75 years old male patient was initiated on prucalopride after many failed treatments for constipation following a Whipple's procedure for pancreatic cancer. Within four months of treatment his creatinine rose from 103 to 285 μmol/L (eGFR 61 decrease to 19 mL/min per 1.73 m^2). He was initially treated with prednisone for presumed acute interstitial nephritis as white blood casts were seen on urine microscopy. When no improvement was detected, a core biopsy was performed and revealed interstitial fibrosis and tubular atrophy. The presence of oxalate and calcium phosphate crystals were also noted. These findings suggest acute tubular necrosis which may have been secondary to acute interstitial nephritis or hemodynamic insult. The use of prednisone may have suppressed signs of inflammation and therefore the clinical diagnosis was deemed acute interstitial nephritis causing acute tubular necrosis. There are no previous reports of prucalopride associated with acute renal failure from the literature, including previous Phase Ⅱ and Ⅲ trials.

Key words: Prucalopride; Acute kidney tubular necrosis; Renal insufficiency; Constipation; Adverse drug event

Core tip: Prucalopride is a novel agent used in the treatment of chronic constipation. We report the first case of acute renal failure secondary to prucalopride four months after treatment initiation. A core renal biopsy after prednisone therapy revealed interstitial fibrosis and tubular atrophy. These findings suggested acute tubular necrosis secondary to acute interstitial nephritis. There are no previous reports of prucalopride associated with acute renal failure from the literature, including previous Phase Ⅱ and Ⅲ trials. This case reports highlights the need for monitoring renal function in all patients treated with prucalopride.

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INTRODUCTION

Chronic constipation is very common and affects 14% of the general population[1]. The incidence rises with age, and is higher in women and those with lower socioeconomic status[2]. It is characterized by infrequent bowel and often associated with abdominal discomfort, bloating and cramps. Patients are susceptible to complications such as hemorrhoids and anal fissures. The consequences on quality of life, health care costs and activity impairment are also significant[3].

The treatment of constipation requires a multifaceted approach which includes lifestyle changes, dietary adjustments, stool softeners, osmotic agents and laxa-

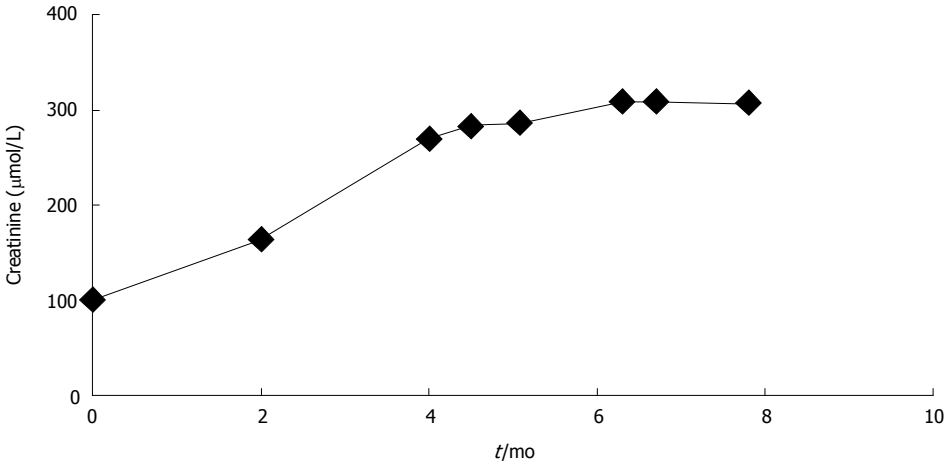

Figure 1 The level of patient's creatinine.

tives[4,5]. Another target for intervention is the 5 hydroxytryptamine-4 (5-HT$_4$) receptor. Until recently, drugs have lacked specificity for the 5-HT$_4$ receptor resulting in an unfavourable risk-benefit ratio with side effects of serious cardiovascular arrhythmias[6,7]. Prucalopride however has demonstrated a high selectivity and affinity for this receptor in the gut with a high efficacy compared to placebo in patients with severe constipation[8-10] and in those who have failed previous laxative therapy[11,12]. The most common adverse effects were headache, nausea, diarrhea and abdominal pain, with no significant cardiovascular effects. Renal failure was not found to be associated with prucalopride and no change in chemical laboratory data was reported from baseline in all of the phase 3 studies[8,12,13]. Randomized trials in elderly patients also found prucalopride to be safe with no effect on renal or cardiac function[10,14]. We report the first case of pruaclopride associated renal failure which was irreversible following discontinuation of the medication.

CASE REPORT

A 75 years old male developed chronic constipation following a Whipple's pancreaticoduodenectomy for pancreatic cancer 19 mo earlier. Over this period, he had multiple emergency room visits for abdominal cramps and pain which were on occasion related to severe constipation and obstipation. He required regular cleansing regimens in hospital, and repeated upper and lower endoscopies revealed no significant pathology. He was referred to a gastroenterologist and his pain resolved with discontinuation of his pancrealipase preparation. After failing several months of therapy for constipation with various bulking, osmotic and stimulant laxatives, he was initiated on prucalopride (Resotran), a new enterokinetic agent, at a dose of 2 mg once daily.

Besides his Whipple's procedure, his surgical history is also significant for an open prostatectomy nine years prior for benign prostatic hyperplasia, remote appendectomy, and a hernia repair. His medical history includes hypertension, dyslipidemia, and a cerebrovascular ischemic stroke with minimal neurologic deficits. His medications at this time were clopidogrel, pantoprazole, candesartan, indapamide, gabapentin, sennoside, as well as 30 g of fiber daily.

The patient was seen four months after the initiation of prucalopride and was now having regular bowel movements for the first time since his Whipple's surgery. He required no further admissions to hospital and his quality of life significantly improved while using prucalopride as the sole agent for management of his constipation. It was however noted that his creatinine was had risen from a baseline of 103 (eGFR baseline 61 mL/min per 1.73 m^2, stable for at least 4 years) to 165 μmol/L (eGFR 35 mL/min per 1.73 m^2) in two months, and further to 270 μmol/L (eGFR 19 mL/min per 1.73 m^2) by four months (Figure 1). He endorsed no symptoms of decreased oral intake, oliguria, abdominal pain, nausea, vomiting, peripheral swelling, or shortness of breath. He also denied any irritative or obstructive urinary symptoms. There were no recent changes to his medications, or any use of over the counter medications such as non-steroidal anti-inflammatory drugs. His candesartan was held and he was referred to a nephrologist for an urgent assessment.

At this appointment he was found to have a normal blood pressure on examination, with no signs of a rash, peripheral edema, or volume overload. His blood work now demonstrated an elevated creatinine of 285 μmol/L at 4.5 mo following prucalopride administration. A complete work up for other renal disease including glomerular based diseases was negative and the patient did not have peripheral eosinophilia. Urinalysis showed +1 proteinuria, trace blood, and urine microscopy revealed many white blood cell casts. An ultrasound of his kidneys showed no signs of obstructive uropathy and Doppler examination of his renal arteries and veins were normal. He was diagnosed with acute interstitial nephritis secondary to his exposure to prucalopride and was instructed to stop this medication. He was started on prednisone 40 mg daily for one week, followed by a taper of 5 mg weekly. The patient was seen in follow-up two weeks later for repeat blood work. Unfortunately his creatinine remained elevated at 310 μmol/L while on prednisone at a dose of 30 mg daily. Given the lack of renal recovery, a renal biopsy

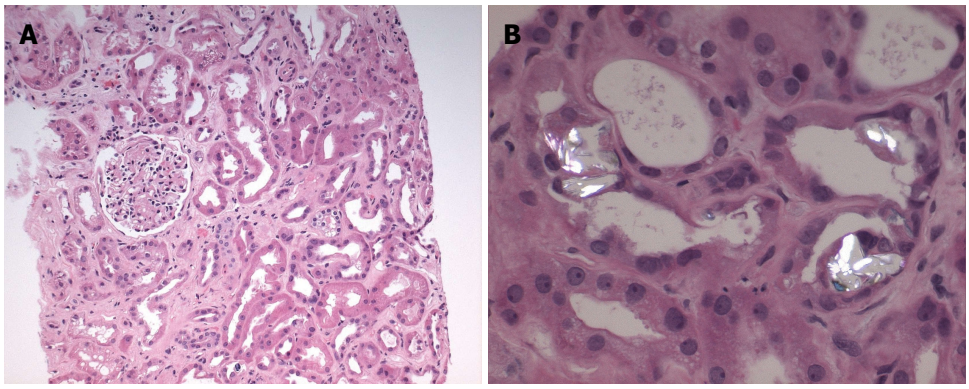

Figure 2 Hematoxylin and eosin stain. A: Hematoxylin and eosin stain demonstrating moderate interstitial fibrosis and tubular atrophy; B: Hematoxylin and eosin stain with polarized light demonstrating calcium oxalate deposition within the tubules.

was performed within one week.

The core biopsy specimen from the left kidney showed 11 of 39 glomeruli globally sclerosed, while the remainder of the glomeruli showed no increase in mesangial matrix or cellularity (Figure 2A). There was minimal interstitial inflammation, with moderate degenerative and regenerative changes within the tubules. There was moderate (40%) interstitial fibrosis and tubular atrophy. There was no arteriolar hyalinosis and moderate arterial sclerosis. Many of the tubules also contained oxalate and calcium phosphate crystals (Figure 2B). Immunofluorescence was negative for immunoglobulin A, G and M, as well as C3, C1q, kappa or lambda. Electron microscopy of the non-sclerosed glomeruli revealed no immune-type deposits, nor any tubuloreticular inclusions. The glomerular basement membranes were mildly wrinkled and within normal limits of thickness. There was moderate effacement of the podocyte foot processes (30%). These findings were consistent with acute tubular necrosis with no evidence for interstitial nephritis.

According to the Naranjo probability score of adverse drug reactions[15], our patient's case was classified as a 'probable adverse drug reaction' of prucalopride induced kidney injury. Points were given for temporal causality, lack of an alternative cause of the reaction, lack of progression with drug discontinuation, and objective confirmation of kidney injury with the renal biopsy.

The patient remained on prednisone at 20 mg daily until seen in follow-up three weeks later. Repeat creatinine remained elevated at 309 μmol/L. His prednisone taper was resumed at 5 mg per week and was ultimately discontinued since there were no signs of ongoing inflammation in the biopsy specimen. The patient unfortunately did not have any further renal recovery and his symptoms of constipation returned while off prucalopride. The search for alternative regimen to treat his chronic constipation is ongoing.

DISCUSSION

Prucalopride is a novel highly selective 5-HT$_4$ receptor agonist developed for the treatment of chronic constipation among patients with an inadequate response to laxatives. The safety of this medication was assessed in all the Phase Ⅱ trials, and in three Phase Ⅲ pivotal trials. A total of 1974 patients were evaluated in the phase Ⅲ trials, with 1313 receiving prucalopride[8,12,13]. The most frequent adverse events reported were headache, abdominal pain, nausea and diarrhea, with most symptoms occurring on the first day. None of the phase Ⅲ trials reported changes in renal function as measured by blood work at baseline and throughout the study. Two smaller placebo-controlled randomized trials in elderly patients with a mean age of 76 and 83, randomized a total of 301 patients to prucalopride[10,14]. The same profile of adverse events were seen in these trials with elderly patients as the larger phase Ⅲ trials. However, in both trials, prucalopride was only administered for 4 wk and while no kidney injury was reported after short-term use, there is a lack of long-term data in the elderly. Numerous other smaller randomized trials with prucalopride also found no associated reports of renal impairment[9,11,16,17]. Elderly patients are at increased risk for baseline renal dysfunction. In the patient described in this report, although stable for least 4 years, the eGFR of 61 mL/min per 1.73 m^2, likely reflected some degree of underlying chronic kidney disease. The elderly patient demographic and potential for underlying chronic kidney disease emphasize the importance of including this group in study trials for safety outcomes.

Our case demonstrates the first report of acute tubular necrosis associated with prucalopride administration. A thorough search on PubMed, Embase and Medline demonstrated no other reports of acute kidney injury secondary to prucalopride. A search for an association with alternative serotonin receptor agonists, such as cisapride or tegaserod, with kidney injury also found no previous case reports. Whether the acute tubular necrosis was due to acute interstitial nephritis or hemodynamic insult cannot be definitively known in this case, since the patient was treated empirically with steroids based on the prominent white blood cell casts on urinalysis. However it remains likely that interstitial inflammation was suppressed by steroid administration prior to the renal biopsy and the working clinical diagnosis was therefore acute interstitial nephritis causing acute tubular necrosis.

The key feature which differentiates prucalopride from other 5-HT$_4$ receptor agonists such as cisapride and tegaserod is its increased selectivity for its receptor[18]. The lack of selectivity of the other older agents resulted

in an appreciable affinity for other receptors, channels or transporters. For example, cisapride had an affinity for the human ether-a-go-go-related gene (hERG) K+ channel found in cardiac cells[19] while tegaserod would also bind to 5-HT_1 and 5-HT_2 receptors[18]. These agents subsequently demonstrated cardiovascular side effects which were independent of their action on the 5-HT_4 receptor[19,20]. The characteristic of high selectivity is important as serotonin receptors are found throughout the body, including the kidney. The primary receptors in the kidney are the 5-HT_2 receptors on smooth muscle cells and the 5-HT_1 receptors on endothelial cells[21]. Stimulation of the 5-HT_2 receptors directly causes renal vasoconstriction, while activation of 5-HT_1 receptors leads to vasodilation indirectly *via* nitric oxide[22]. It has been found that administration of serotonin impairs autoregulation of the glomerular filtration rate of the kidney, leaving it vulnerable to ischemic damage[23]. While prucalopride has agonistic effects on the serotonin receptor, given that it has not been shown to activate the specific subtypes of 5-HT_2 and 5-HT_1, this mechanism of kidney injury is less likely. It is not known whether the concurrent use of candesartan in this patient may have also played a role in the development of acute tubular necrosis, since angiotensin Ⅱ blockade can also cause impaired renal autoregulation and a decline in glomerular filtration rate through postglomerular vasodilatation.

Our patient's renal biopsy also demonstrated increased deposition of crystals, with predominantly oxalate crystals as well as calcium phosphate crystals. Increased absorption of oxalate from the colon occurs in fat malabsoprtion states, such as pancreatic insufficiency[24]. In such instances, calcium preferentially binds to free fatty acids instead of oxalate, which allows the free soluble oxalate to be absorbed through the colon. Other factors which can increase oxalate absorption include the presence of bile salts[25] and the absence of bacteria such as *Oxalobacter formigenes* and certain strains of *Entercoccus fecalis* which are able to degrade oxalate[26]. Our patient had discontinued his pancrealipase preparation at the time prucalopride was started due to side effects of abdominal pain. Given his history of Whipple's pancreatectomy and the discontinuation of his pancreatic replacement enzymes, this fat malabsorption state may have induced hyperoxaluria.

Oxalate nephropathy can occur from tubular obstruction caused by calcium oxalate crystals, or by direct tubular injury which results in progressive tubular atrophy and interstitial fibrosis[25]. It is also common to see small numbers of oxalate crystals within tubules after acute tubular necrosis as well as in other chronic renal impairment conditions. Given the mixture of both oxalate and calcium phosphate crystals in our patient's renal biopsy, an underlying oxalate nephropathy as the etiology of the acute kidney injury is less probable. In addition, the creatinine stabilized with cessation of prucalopride and the patient did not yet resume his pancrealipase preparation. Cases of oxalate nephropathy reported in the literature are often associated with oliguria and a marked decline in renal function requiring hemodialysis[27]. Fortunately, our patient's renal failure was not as severe. Follow up urinalyses have failed to demonstrate crystals of any type, further suggesting that a crystal nephropathy is not playing an important contribution to the patient's renal failure. Furthermore, high-fluid intake and low oxalate diet recommendations along with calcium carbonate supplements have not been associated with improved renal function.

In conclusion, given the lack of literature to support prucalopride and other serotonin receptor agonists as nephrotoxins, our patient's case of acute renal failure was treated initially as allergic interstitial nephritis. However, when his renal function did not improve with discontinuation of the medication and prednisone therapy, a renal biopsy was performed to confirm the diagnosis. This case demonstrates the importance of a renal biopsy when the diagnosis is unclear or when there is lack of improvement with therapy. In addition, this case also highlights the importance of routine blood work to follow cell count, biochemistry and renal function when starting a medication which is new to both the patient and the medical community. Adverse effects which were not documented by clinical trials may still occur in our patients and reporting of such outcomes is required for ongoing drug safety and monitoring. In addition, given the limited long-term data available for elderly patients, and unreliability of serum creatinine in estimating renal function, a lower 1 mg of prucalopride should be initiated in this population. Without routine blood work, this case of renal failure may have been missed until the patient presented with more significant symptoms related to renal failure such as oliguria, vomiting, volume overload or uremia.

COMMENTS

Case characteristics

A 75 years old gentleman initiated on prucalopride for chronic constipation with subsequent elevation of serum creatinine from 100 μmol/L to 270 μmol/L within four months.

Clinical diagnosis

He was treated with prednisone for presumed acute interstitial nephritis and a subsequent renal biopsy demonstrated acute tubular necrosis secondary to acute interstitial nephritis.

Differential diagnosis

Acute interstitial nephritis secondary to a drug allergic reaction, oxalate nephropathy, and acute tubular necrosis following hemodynamic insult, angiotensin Ⅱ blockade or interstitial nephritis.

Laboratory diagnosis

Serum creatinine rose from a baseline of 103 μmol/L to a peak of 310 μmol/L and urine microscopy revealed many white cell casts.

Imaging diagnosis

Abdominal ultrasound showed no signs of obstructive uropathy, and Doppler examination was negative for renal artery stenosis.

Pathologic diagnosis

A renal biopsy was performed after cessation of prucalopride and administration of prednisone revealing moderate interstitial fibrosis and tubular atrophy with deposition of oxalate and calcium phosphate crystals.

Treatment

Therapy with prednisone was initiated once white cell casts were seen on uri-

nary microscopy and prucalopride was discontinued resulting in stabilization of the serum creatinine but no further recovery of renal function.

Related reports

This is the first case of acute renal failure reported in the literature, with no previous occurrences documented from several previous Phase II and III trials.

Term explanation

Prucalopride is a novel highly selective 5 hydroxytryptamine-4 receptor agonist developed for the treatment of chronic constipation after failure of laxative therapy.

Experiences and lessons

This case highlights the need for monitoring of routine blood work with cell count, biochemistry and renal function when using medications new to both the patient and the medical community as previously undocumented adverse events may develop.

Peer review

This is an important case report in regard to clinical use of prucalopride.

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CASE REPORT

Actinic prurigo of the lip: Two case reports

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Author contributions: Miranda AMO, Ferrari TM, Werneck JT, Silva Junior A were involved in patient care; Miranda AMO and Ferrari TM collected the patient's clinical data and wrote the paper; Miranda AMO and Dias EP designed the report; Cunha KS and Werneck JT translated the paper; Cunha KS and Dias EP drafted the article, revised it critically for important intellectual content and approved the final version to be published.

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Abstract

Actinic prurigo is a photodermatosis that can affect the skin, conjunctiva and lips. It is caused by an abnormal reaction to sunlight and is more common in high-altitude living people, mainly in indigenous descendants. The diagnosis of actinic prurigo can be challenging, mainly when lip lesions are the only manifestation, which is not a common clinical presentation. The aim of this article is to report two cases of actinic prurigo showing only lip lesions. The patients were Afro-American and were unaware of possible Indian ancestry. Clinical exam, photographs, videoroscopy examination and biopsy were performed, and the diagnosis of actinic prurigo was established. Topical corticosteroid and lip balm with ultraviolet protection were prescribed with excellent results. The relevance of this report is to show that although some patients may not demonstrate the classical clinical presentation of actinic prurigo, the associated clinical and histological exams are determinants for the correct diagnosis and successful treatment of this disease.

Key words: Actinic prurigo; Follicular cheilitis; Photodermatosis; High-altitude; Lip diseases

Core tip: The diagnosis of actinic prurigo can be challenging in the absence of classic clinical manifestations. Actinic prurigo is found in high-altitude living people, mainly in indigenous descendants. Disease onset is usually in childhood and rarely presents only on the lips. This study describes two rare cases from Rio de Janeiro city, Brazil, which is located at sea level. The patients were unaware of possible Indian ancestry. Moreover, actinic prurigo appeared in adulthood and lip lesions were the only manifestation. The associated clinical and histological exams are determinants for the correct diagnosis and successful treatment of this disease.

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INTRODUCTION

Actinic prurigo (AP) is a type of photodermatosis, and is a rare familial inflammatory disease that primarily affects areas of skin exposed to the sun and can affect the lips and ocular conjunctiva (pseudopterygium formation)[1]. Pseudopterygium does not appear as a unique lesion in patients with AP, it is always preceded by skin and lip lesions, suggesting that this expression tends to appear later in the disease course. For this reason, the diagnosis of AP in its early stages is important to prevent subsequent complications[2]. AP of the lip, also known as follicular cheilitis, is mainly found on the vermillion of the lower lip. Lip lesions may appear early in the development of

this disease and, consequently, its observation and accurate diagnosis can alert physicians or dentists to the possible development of other more severe lesions on the skin or conjunctiva[2]. AP occurs mainly in residents of high altitudes and affects ethnic groups, particularly in North and South America, who express major histocompatibility complex class I and Ⅱ (HLA I and Ⅱ), suggesting a genetic predisposition[3]. The aim of this article is to describe two cases of AP of the lips without the classical features of this disease (young age at onset, familial history, high-altitude living people, and an association with skin lesions).

CASE REPORT

Case one

A 63-year-old Afro-American woman presented to our Oral Diagnostic clinic complaining of lower lip lesions of 10 mo evolution, which had worsened in the last 6 mo. She was referred by two centers that had failed to establish the diagnosis. During physical exam, the lower lip showed edema, as well as multiple ulcers covered with yellowish crusts on the semimucosa (Figure 1A). The slightest touch or mouth opening resulted in significant bleeding, which, according to the patient was commonly observed. No alterations during intraoral examination were observed. The lesions were documented by clinical and videoroscopy images (Figure 1B) and were scraped for cytopathologic evaluation, which revealed moderate inflammation. Lip balm with ultraviolet (UV) protection was prescribed.

On the second visit, debridement of the lesions was performed, as well as a biopsy (the selected area was chosen by clinical and videoroscopy exam) (Figure 1C). The clinical diagnostic hypotheses were erythema multiforme and contact cheilitis. Microscopically (Figure 1E-H), the surface epithelium showed orthokeratosis, with some areas of parakeratosis, atrophy and areas of acanthosis, as well as basal layer degeneration and lymphocytic exocytosis. Ulceration was also present. The connective tissue exhibited pigmentary incontinence close to the overlying epithelium, dilated blood vessels, edema and intense and diffuse lymphocytic inflammatory infiltrate, with some plasma cells, extending deep into the fatty tissue. Some secondary lymphoid follicles were also present. Several mast cells were present predominantly in the deeper area of the connective tissue, mainly in the perivascular and perineural areas. Nonspecific chronic sialadenitis with ductal ectasia was also observed. There was no solar elastosis. The diagnosis of follicular cheilitis was established.

Following diagnosis, a combination of triamcinolone acetonide cream, neomycin sulfate, gramicidin and nystatin cream was prescribed three times a day. The patient was instructed to use gauze compresses with cold physiological saline and to continue using lip balm with UV protection. The patient was also referred to the dermatology and ophthalmology service for evaluation of signs and symptoms of AP. No ocular or skin lesions were observed.

Complete remission of the lip ulcers and crusts was observed after one month of treatment (Figure 1D). The patient was followed-up monthly for three months without evidence of recurrence. Two months after diagnosis and during the follow-up period, the patient reported she was of indigenous Brazilian descent. After the third consecutive monthly follow-up, the patient was followed-up every 4 mo to date (2 years after the first visit), and showed no lip lesions (Figure 1D). The patient did not develop any skin or ophthalmic lesions.

Case two

A 58-year-old Afro-American woman, presented to our Oral Diagnostic clinic complaining of a painful lesion on the lower lip of four years evolution. Physical examination showed the presence of a yellowish crust of 1.3 cm × 0.8 cm, on the left side, which was easily seen during the examination, revealing an ulcerated area. The lips were swollen and dry (Figure 2A). The lesions were documented by clinical and videoroscopy images (Figure 2B) and were scraped for cytopathologic evaluation, which revealed moderate inflammation. No alterations were observed during the intraoral examination. Lip balm with UV protection was prescribed. On the second visit, a biopsy was performed (the selected area was chosen by clinical and videoroscopy exam). The diagnostic hypotheses were erythema multiforme and acute actinic cheilitis. Microscopically (Figure 2C and D), the lesion was covered by stratified ortokeratinized squamous epithelium showing atrophy, ulceration, spongiosis and hydropic degeneration of the basal layer. The underlying connective tissue showed pigmentary incontinence close to the overlying epithelium, dilated blood vessels with areas of intense inflammatory infiltrate, mainly composed of lymphoplasmacytic cells, and the formation of well-formed secondary lymphoid follicles. Mast cells were also observed between the lymphocytes and plasma cells. The inflammatory infiltration extended deep into the fatty tissue. There was no solar elastosis. The diagnosis of follicular cheilitis was established.

The patient was followed-up (one month after the first visit) and showed remission of the ulceration on the left side, with only a small ulcer on the right side of the lip (Figure 2B). She was referred for dermatological and ophthalmological evaluation and asked to return to our clinic one month later. The patient did not return.

A search of the medical literature was performed by two authors separately, using Pubmed, Lilacs, Scielo and Cochrane databases, without year and language restriction, using the terms: (1) prurigo AND actinic; and (2) follicular AND cheilitis. The last search was performed in November 2013. A paper considered eligible for inclusion on review had to include a case report or a study with at least one case under the name "actinic prurigo" or "follicular cheilitis" and with lip lesions as the only manifestation (Table 1). Only two papers satisfied the criteria: Vega-Memije *et al*[2] and Mounsdon *et al*[4]. In the

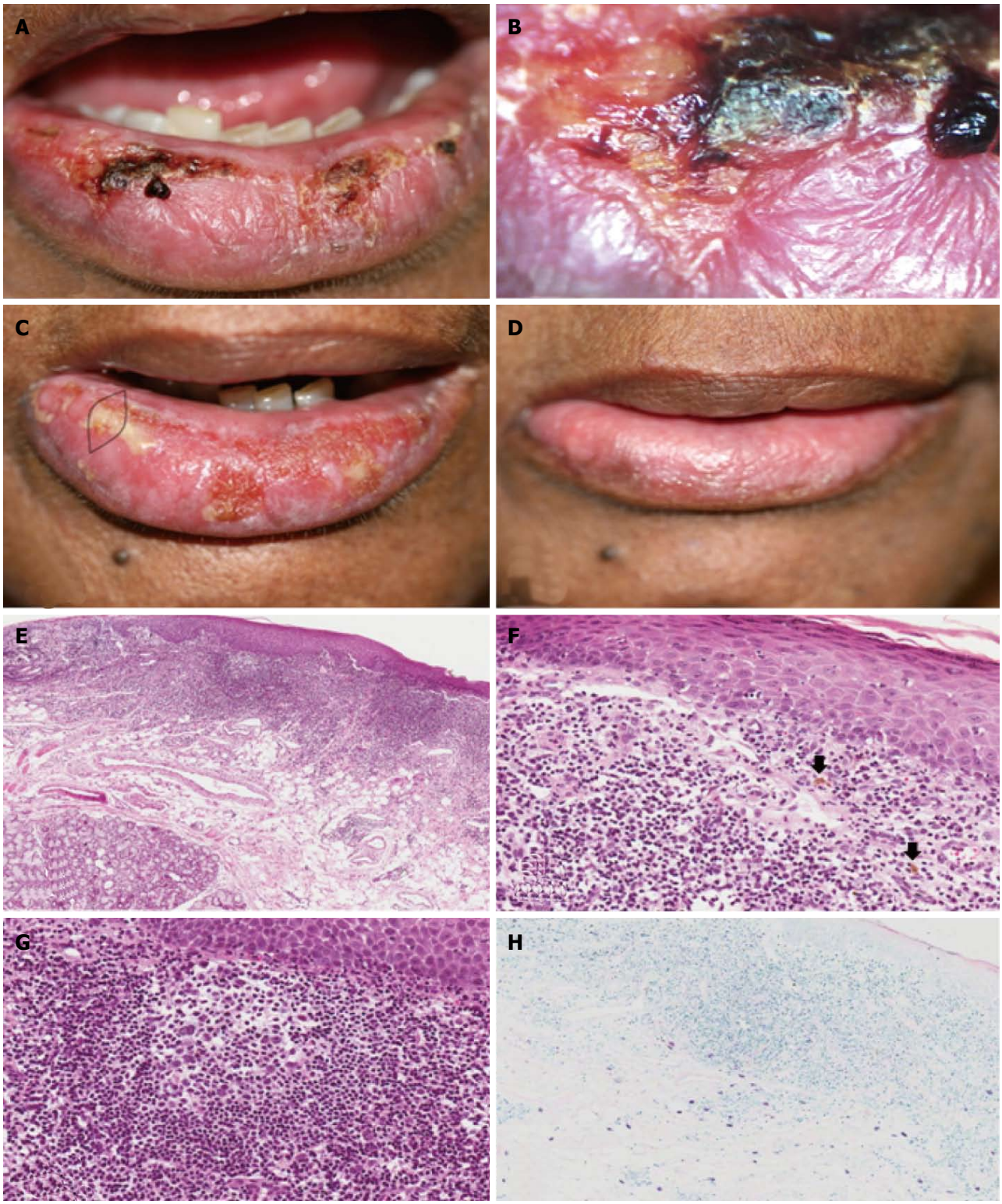

Figure 1 Case 1. A: Clinical aspect at the first appointment, showing lower lip edema, ulcers and crusts; B: Videoroscopy image showing in detail the presence of ulcer and crust; C: Clinical aspect at the second appointment showing the area of biopsy; D: Clinical aspect one month after treatment, showing remission of the lip edema, ulcers and crusts; E: Histological aspects. Epithelial atrophy and intense diffuse lymphoplasmacytic inflammatory infiltrate extending deep into the fatty tissue (× 10, HE); F: Epithelium showing spongiosis, hydropic degeneration of the basal layer cells and lymphocytic exocytosis. In the connective tissue, lymphocytic inflammatory infiltrate and pigmentary incontinence (arrows) were observed (× 40, HE). G: Secondary lymphoid follicle (× 40, HE); H: Mast cells mainly in the deeper area of the connective tissue (× 20, Giemsa).

study by Vega-Memije *et al*[2], 116 patients presented with actinic prurigo cheilitis; of these, 74 (63.8%) were female, aged from 9 to 82 years (mean, 27.8 years). Ninety-nine percent of the patients lived in areas more than 1000 m above sea level and only one case was from a geographic area below this altitude. AP cheilitis was the only manifes-

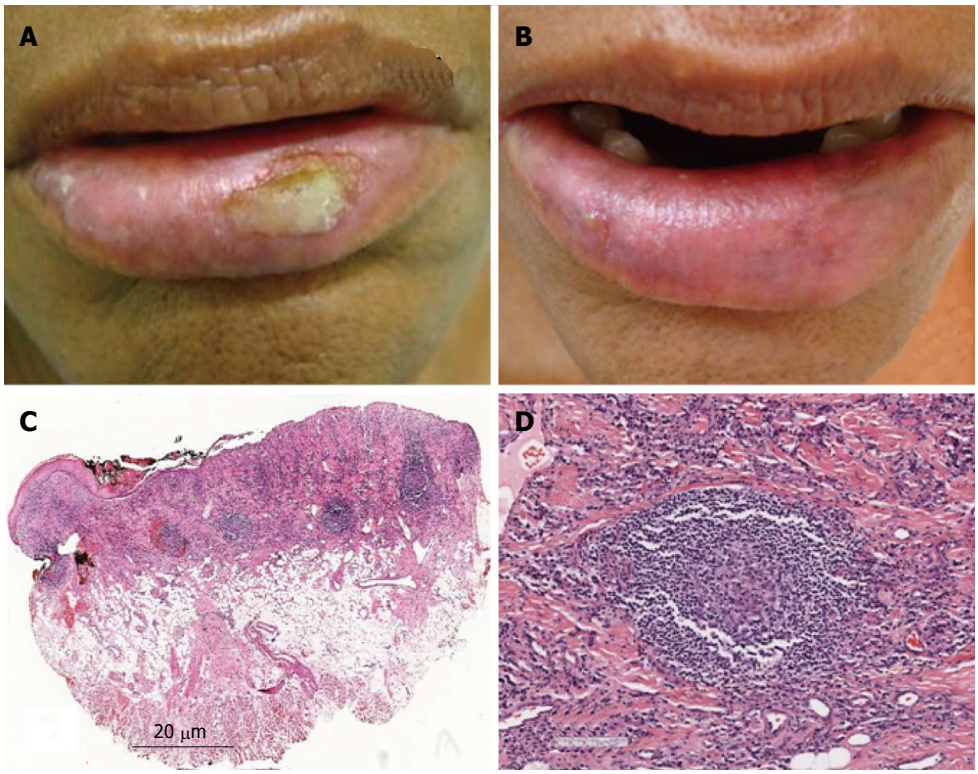

Figure 2 Case 2. A: Clinical aspect at the first appointment, showing lower lip edema, dryness and ulcer on the left side of the semimucosa; B: Clinical aspect at the second appointment, showing remission of the ulceration on the left side, and only a small ulcer on the right side of the semimucosa; C: Histological aspects. Lower power view showing epithelial atrophy and ulceration. In the connective tissue, an intense, diffuse inflammatory infiltrate extending deep into the fatty tissue, with some lymphoid follicles was observed (HE); D: Secondary lymphoid follicle (HE).

Table 1 Results of the literature search for "actinic prurigo" or "follicular cheilitis" of the lip

	Actinic prurigo	Follicular cheilitis	Eligible paper[1]
Pubmed	143	9	2
Lilacs	25	0	0
Scielo	3	0	0
Cochrane	7	1	0

[1]A paper considered eligible for inclusion in the review had to include a case report or a study with at least one case under the name "actinic prurigo" or "follicular cheilitis", and show lip lesions as the only manifestation.

tation of the disease in 32 (27.6%) patients. Mounsdon *et al*[4] described two North American Indians, one man and one woman, who showed only lip lesions, however, there was no information on their place of residence. In addition, a thesis describing a study of 43 patients with actinic prurigo of the lips was found in Google Scholar[5]. Although this study was carried out in Brazil, it was a retrospective analysis of patients resident in Mexico, where this disease is very common. In 17 (39.54%) cases, the lesion was located only on the lips. To make comparative analyses with the cases presented in our paper, 16 patients in this study were included; one was excluded because the age of the patient was not provided. Patient age ranged from 11 to 63 (mean 26 years). Information on where the patients lived was not provided (Table 2).

DISCUSSION

Photodermatoses form an important group of skin diseases, which can be disabling to the patient, and represent a challenge in diagnosis and treatment[6]. Although dark skin has larger quantities of melanin compared to white skin, which gives greater protection against the sun's rays, photodermatoses are common in dark-skinned people[7]. AP is an example of a photodermatosis that affects mostly Mestizos in the Americas. This is the result of miscegenation between Europeans and Indians, which prevails in Mexico, Guatemala, Honduras, Colombia, Ecuador, Peru, Bolivia, and Argentina, and in some indigenous communities in North America and Canada[8-10]. AP usually begins in childhood, around 4-5 years old[5], although it can manifest at any age, affecting more women than men (2:1), and in some cases with familial history[11].

The severity of the disease is altitude-dependent, presumably because of the sustained intensity of sun exposure. It is believed that this is the reason why AP is found mostly in regions with altitude above 1000 m[3]. These data make our cases interesting, as both patients lived in Brazil, in cities at sea level, and did not report being indigenous descendants during anamnesis, did not have a positive familial history, and showed the first signs and symptoms in adulthood.

AP lesions are mainly found in sun-exposed areas[3,12,13]. Lips and conjunctiva can also be affected[3,12].

Table 2 Data from patients with actinic prurigo, with only lip lesions

	Vega-Memije *et al*[2]	Rizo *et al*[5]	Mounsdon *et al*[4]	Maga-a *et al*[1]
Age	9-82 (mean 27.8 yr)	11-63 (mean 26 yr)	61 and 69 yr old	58 and 63 yr old
Country	Mexico	Mexico	United States (North American Indians)	Brazil
High altitude	99% more than 1000 m	Unknown	Unknown	Sea level

Nevertheless, in Asians, conjunctivitis and cheilitis are not common[14]. The patients presented in this paper showed lip lesions as the only manifestation of AP. Although there are few reports and studies in the literature regarding patients with AP showing only lip lesions, this may occur in up 40% of cases[5]. In cases of AP with lip lesions as the only manifestation it is more difficult to establish an accurate diagnosis, which should alert clinicians to the possibility of the development of other more severe lesions, such as skin or conjunctival lesions. Therefore, it is important to refer these patients for ophthalmological and dermatological evaluation.

AP lip lesions are characterized by swelling, peeling, cracking, crusting, itching, exudation, and secondary ulceration[3,12]. Cheilitis intensity is variable. In the acute phase, yellow crusts adhered to the surface are observed, whereas in the chronic phase, the lesions are covered with dry scales, and the course is generally prolonged, with relapses worsened by constant sun exposure[2,8,5].

During the evaluation of our patients, we used videoroscopy which enabled better visualization of the lip lesions. As both patients showed extensive lesions, the choice of the biopsy area was difficult and videoroscopy was used to help choose the best biopsy area. The lesions were similar to those of AP lip lesions described in the literature.

Clinical differential diagnoses regarding AP include actinic cheilitis, frictional contact cheilitis and granulomatous cheilitis[5]. In the present cases, we also considered the possibility of acute actinic cheilitis, which was later rejected due the evolution time and because the patients did not report intense sunlight exposure. The other clinical diagnoses were erythema multiforme, which was rejected due to the course of the lesions, and contact cheilitis, but we were unable to identify a substance which could cause the lip lesions, especially over such a long time. Although several clinical factors associated with follicular cheilitis were not observed in the present cases, the clinical exam associated with the histopathological diagnosis was a determinant in establishing the final diagnosis.

Studies in the literature define the histopathological pattern of AP lip lesions as showing acanthosis, spongiosis and basal layer hydropic degeneration[2]. Areas of ulceration may also be seen. Edema, dilated and congested vessels, with dense predominantly lymphocytic inflammatory infiltrate, which may contain lymphoid follicles and eosinophils are also seen in the connective tissue[2,4,12]. Furthermore, some studies report that discrete exocytosis in the basal epithelium and pigmentary incontinence in the sub epithelial connective tissue may be observed[2]. The presence of lymphoid follicles is considered by some authors to be a pathognomonic feature of AP and this is the reason why the term follicular cheilitis is used[12]. Mast cells and macrophages may be found in the inflammatory infiltrate[5]. The histopathological findings in our cases are consistent with the description in the literature. The identification of lymphoid follicles in both cases was important in establishing the diagnosis.

No solar elastosis was found in the AP lesions, which facilitates the differential diagnosis from actinic cheilitis[2,4,5,12]. It is necessary to differentiate AP from polymorphic light eruption, which is clinically similar, but microscopically does not show lymphocytic infiltrate with lymphoid follicles[12].

With regard to the treatment of AP, as a general measure, it is recommended to reduce sun exposure, use protective clothing including hats, and sunscreen. However, these measures are not sufficient to treat AP. There is evidence that AP is an autoimmune disease, and therefore immunosuppressive drugs produce good results[3]. Treatment of AP varies according to the severity and extent of the lesions, and includes topical and systemic corticosteroids to reduce the inflammation and itching of active lesions, antibiotics for secondary infections, antihistamines, antimalarials and thalidomide, which have been shown to be the most effective drugs for the treatment of AP[12,15-18].

AP prognosis is not good, despite several treatment options, the lesions may have a chronic course and are difficult to control if patients live in sunny areas, are occupationally exposed to the sun or live in high altitudes[19]. In case 1, the patient responded well to treatment with a topical corticosteroid and prevention measures; she had no lesions up to the last follow-up (14 mo after diagnosis). The patient in case 2 was treated only with prevention measures (including the use of lip balm with UV protection). In the follow-up, one month after diagnosis, the lesions disappeared, but she did not return for her follow-up appointment.

AP is a well-known disease, occurring mainly in Mestizos, living in high altitudes with onset during childhood. The cases presented here were a challenge to diagnose as the clinical characteristics were different from the classical manifestations of AP: the lesions began in adulthood, the patients lived at sea level and did not report, at least during the interview, being indigenous descendants, and neither reported having a familial history of alterations. In these cases, without skin lesions, the diagnosis of AP in the early stages is important, as it can alert the clinician to the possible development of other more severe le-

sions, and, thus, referring the patients for an ophthalmologic and dermatologic evaluation is mandatory.

COMMENTS

Case characteristics

This paper reports two cases of actinic prurigo in which the lower lips were the only sites of involvement.

Clinical diagnosis

The relevance of these cases is that, although some important aspects do not follow the classical features of actinic prurigo, the associated clinical and histological exams can be determinants of the correct diagnosis and successful treatment.

Imaging diagnosis

Clinical exam, photographs, videoroscopy examination and biopsy were performed, and the diagnosis of actinic prurigo was established.

Peer review

It is an interesting case, it is well written.

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CASE REPORT

Appendicitis in double cecal appendix: Case report

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Author contributions: Alves JR conducted the patient care in the emergency, surgery and photography service during the intraoperative period (Figure 1) and the postoperative medical care, was in charge of general supervision of students, writing, translation, final review and article submission; Maranhão IGO, Oliveira PVV performed the literature review on the anatomical variations of the cecal appendix, and are co-authors of the manuscript. All the authors read and approved the final manuscript.
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Abstract

Double cecal appendix is a rare anatomical variation. Approximately 100 cases have been reported worldwide. It is usually diagnosed incidentally during emergency appendectomies due to inflammatory processes in the cecal appendix. Case presentation: male, white, 36 years old, obese, presenting with pain in the lower abdomen for 24 h followed by nausea, vomiting and mild fever. He was subjected to additional tests, with the leukogram showing leukocytosis and abdominal ultrasonography depicting cecal appendix with thickened wall, locally associated with small quantities of liquid and intestinal loop obstruction. He underwent laparotomy, revealing acute appendicitis. Another intestinal loop obstruction was identified next to the ileum, leading to recognizing another cecal appendix after local dissection. Double appendectomy and segmental iliectomy were performed although not needed. Results of the anatomopathological examination of the surgical samples showed acute inflammation in the two cecal appendices. So, performing a routine retroperitoneal release and a complete cecum evaluation during such surgical procedures is recommended and suggested due to the possibility of not identifying a second cecal appendix.

Key words: Appendix; Anatomic variation; Appendicitis; Appendectomy; General surgery

Core tip: Double cecal appendix is a rare (about 100 cases reported worldwide) anatomical variation often incidentally diagnosed in the face of inflammation in the organ. The current paper presents the first case reported in South America. The case is extremely important for the study of this possible anatomical variation since the lack of a diagnosis in a second cecal appendix can cause further complications for the patient and the physician. Moreover, it is associated with the presence of other anatomical variations, such as intestinal, genitourinary and bone. Such variations will be investigated in cases of the aforementioned diagnosis.

Alves JR, Maranhão IGO, Oliveira PVV. Appendicitis in double cecal appendix: Case report. *World J Clin Cases* 2014; 2(8): 391-394 Available from: URL: http://www.wjgnet.com/2307-8960/full/v2/i8/391.htm DOI: http://dx.doi.org/10.12998/wjcc.v2.i8.391

INTRODUCTION

Double cecal appendix is a rare anatomical variation, found in 0.004%[1] to 0.009%[2] of performed appendectomies. Approximately 100 cases of double cecal appendix[3-5] have been described worldwide so far, with no case reports in South America[2,3,6-37].

CASE REPORT

A male, white, 36 years old, slightly obese [body mass

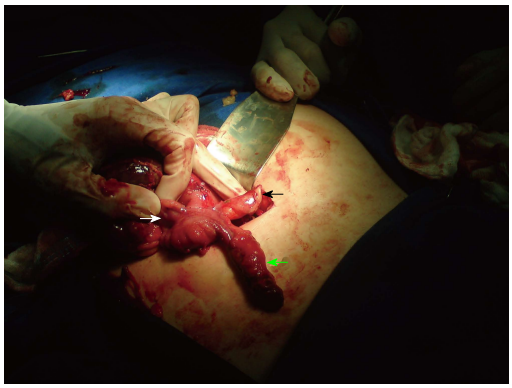

Figure 1 A photograph taken during a laparotomy procedure depicting an inflamed double cecal appendix. Minor (black arrow) and major (green arrow) inflamed cecal appendix. Surgeon's hand is on the left side of the picture, holding the proximal segment of the ileum (arrow with white edges).

index (BMI) = 31.1 kg/m^2], presented with abdominal pain in the lower abdomen for 24 h, followed by nausea, vomiting and mild fever (axillary temperature = 37.9 ℃). He was subjected to blood tests that only showed leukocytosis without left shift. In addition, abdominal ultrasonography depicted cecal appendix with thickened wall, locally associated with small quantities of intra-abdominal fluid and local obstruction of intestinal loops.

He underwent laparotomy with a McBurney's incision. The presence of an inflamed cecal appendix in its usual position after lysis of adhesions and cecum release was identified. Another intestinal loop obstruction was identified near the ileum. After the release of dense adhesions, it was possible to recognize the presence of a second cecal appendix, also with an inflammatory aspect (Figure 1), with its origin along the taenia coli.

A double appendectomy and segmental iliectomy in the part of the devascularized intestinal loop, resulting from ileum dissection, was performed in order to provide the release and excision of the second cecal appendix. Both appendices showed no sign of perforation despite the inflammatory aspect, *i.e.,* the occurrence of increased dimensions, thickened and erythematous wall, associated with fibrin and local tissue fragility.

The anatomopathological examination of the surgical samples corroborated the diagnosis of inflammation in both cecal appendices and resected segment of small intestine (ileum), with subserosal congestion and acute fibrinous serositis with eosinophils.

The patient had no postoperative complications and was discharged on the third day after surgery.

DISCUSSION

Since 1892 after the first case of double cecal appendix[27] was reported, less than 100 cases have been reported worldwide[3]. It demonstrates the rarity of such variations and why the current reported case is the first one to be described in South America[2,3,6-37].

Over time, some authors have presented classifications to categorize anatomical variations of cecal appendix. The first classification was developed in 1936 by Cave[28]. His classification was modified in 1962 by Wallbridge[29]. Since then, a number of authors have made some changes to it, leading to the modified classification by Cave-Walbridge, which is now the most widely used[17,30].

The classification modified by Cave-Wallbridge categorizes double cecal appendix into three types: A, B and C. Type A is characterized by the presence of two cecal appendices with a common origin in a single cecum. In type B, two appendices emerge from different cecal origins from a single cecum. This type is also subdivided into B1 and B2. In subtype B1, the two appendices emerge from a single cecum, one from each side of the ileocecal valve, symmetrically. On the other hand, in subtype B2, one of the appendices is in its usual position and the second one is located alongside the taenia coli. Finally, type C is characterized by the existence of two caeca, each with a cecal appendix (Figure 2).

The present reported case describes the occurrence of a patient with double cecal appendix type B. There are reports of other rarer forms presenting with anatomic variations of the cecal appendix, such as the horseshoe appendix[31] and the triple appendix[32].

The existence of an cecal appendix duplication is asymptomatic and its diagnosis only comes during investigations on inflammation processes[3,17,33,34]. This is what happened in our patient's case. According to clinical data, he had no complaints related to his cecal appendix duplication until the occurrence of acute appendicitis.

Despite the rarity of anatomical variations in the cecal appendix, the awareness of them is of great importance to surgeons. An inadequate surgical evaluation of the cecum due to unawareness of such variations can leave a second or third cecal appendix[17,30] unidentified. This may lead to further reoperations, diagnostic difficulties and medicolegal problems regarding malpractice because of the possibility of new inflammation in the remaining appendices[17,30].

For instance, this happened in a child whose cecal appendix duplication was not identified in the first appendectomy. Five months later, another laparotomy was needed in order to remove a second appendix which had also become inflamed[35]. Such a situation is most commonly found in patients with double cecal appendix type B[30]. It is worth mentioning that there is an increase in the postoperative morbidity and mortality[17,30] in patients in whom anatomical variations of the cecal appendix are not identified.

Finally, the importance of being aware of the association between double or triple cecal appendix and other anatomical variations, intestinal, genitourinary and osseous, should be highlighted[36,37]. These are most often associated with duplications of the cecal appendix types B1 and C[3]. Thus, when two or three cecal appendices are identified, investigating these other anatomical variations is recommended[3].

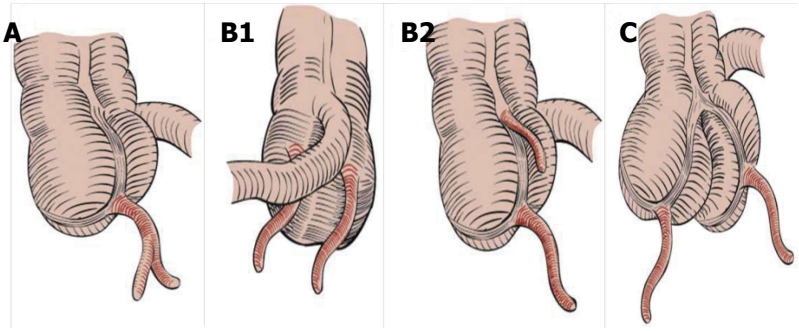

Figure 2 Classification modified by Cave-Wallbridge[30], including type A, subtype B1, subtype B2 and type C.

As a final conclusion, although double or triple cecal appendices are rare, surgeons must be aware of them and identify cecal appendix anatomical variations. Such a procedure is recommended when doctors surgically approach a patient with acute appendicitis. They should perform a complete cecum evaluation after the retroperitoneal release in order to avoid further complications. Surgeons should remember that in the face of such changes, they will need to investigate the presence of intestinal, genitourinary or bone anatomic variations.

ACKNOWLEDGEMENTS

We thank the patient for allowing the disclosure of his medical report and intraoperative photographic records.

COMMENTS

Case characteristics

Male, white, 36 years old, slightly obese, presenting with acute appendicitis.

Clinical diagnosis

Abdominal pain in the lower abdomen for 24 h, followed by nausea, vomiting and mild fever (axillary temperature = 37.9 ℃).

Differential diagnosis

Causes of acute inflammatory abdomen.

Laboratory diagnosis

Leukocytosis without left shift.

Imaging diagnosis

Abdominal ultrasonography depicting cecal appendix with thickened wall, locally associated with small quantities of intra-abdominal fluid and intestinal loop local obstruction.

Pathological diagnosis

Inflammation in both cecal appendices.

Treatment

Laparotomy with a McBurney's incision, followed by the performance of a double appendectomy and segmental iliectomy.

Related reports

Double cecal appendix is a rare (about 100 cases reported worldwide) anatomic variation most often incidentally diagnosed in face of inflammation of that organ.

Term explanation

The classification modified by Cave-Wallbridge categorizes double cecal appendix.

Experiences and lessons

The surgeon must be aware and identify cecal appendix anatomical variations. The procedure is recommended when surgeons surgically approach a patient with acute appendicitis. It is worth performing a complete cecum evaluation after the retroperitoneal release.

Peer review

This case report is well designed and presents a wide range of information about the subject, spreading the right messages and broadly contributing to the literature.

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CASE REPORT

Rare large homozygous *CFTR* gene deletion in an Iranian patient with cystic fibrosis

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Abstract

Cystic fibrosis, a common autosomal recessive genetic disorder among Caucasians, is caused by defects in the transmembrane conductance regulatory (*CFTR*) gene. The analysis of *CFTR* gene mutations is useful to better characterize the disease, and for preconceptional screening, prenatal and preimplantation genetic diagnosis. Here we report the results of a genetic analysis in a 16-year-old boy from southwestern Iran diagnosed as having cystic fibrosis in infancy based on gastrointestinal and pulmonary manifestations, with positive sweat chloride tests. He lacked both normal and mutant forms of the fragment corresponding to the ΔF508 allele in initial genetic studies. Multiplex ligation-dependent probe amplification-based testing revealed a homozygous deletion spanning exons 4 to 10 of the *CFTR* gene. We predict an in-frame deletion removing 373 amino acids based on our sequencing results. Determining *CFTR* gene mutations in patients and their family members would be helpful to prevent the occurrence of new cases, especially in populations in which consanguinity is common.

Key words: Cystic fibrosis; Transmembrane conductance regulatory gene; Homozygous deletion

Core tip: Genetic analysis of the transmembrane conductance regulatory (*CFTR*) gene is helpful to characterize patients with cystic fibrosis, but sequencing and multiplex ligation-dependent probe amplification-based testing are only done to diagnose rare or unknown variants. Here we report a 16-year-old boy, the son of consanguineous healthy parents, who lacked both the normal and mutant forms of the ΔF508 alleles in initial molecular tests. Further analysis disclosed a rare large homozygous *CFTR* gene deletion in this patient.

Farjadian S, Moghtaderi M, Zuntini R, Ferrari S. Rare large homozygous *CFTR* gene deletion in an Iranian patient with cystic fibrosis. *World J Clin Cases* 2014; 2(8): 395-397 Available from: URL: http://www.wjgnet.com/2307-8960/full/v2/i8/395.htm DOI: http://dx.doi.org/10.12998/wjcc.v2.i8.395

INTRODUCTION

Cystic fibrosis (CF), a common autosomal recessive genetic disorder among Caucasians, is caused by defects in the transmembrane conductance regulatory (*CFTR*) gene. This gene spans more than 250 kb on chromosome 7q31.2 and comprises 27 exons encoding a 170 kDa chloride channel expressed exclusively in secretory epithelial

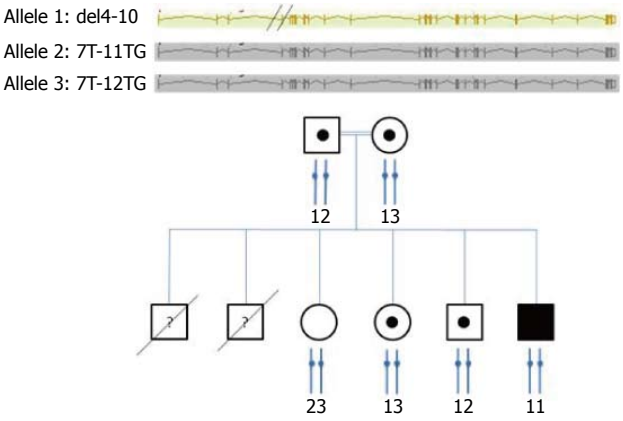

Figure 1 Pedigree of a family of a 16-year-old boy with cystic fibrosis, showing the three transmembrane conductance regulatory alleles transmitted to the sibs. Allele 1 carries the deletion of exons 4 to 10; alleles 2 and 3 are distinguishable by the different numbers of TG associated to the polypyrimidine tract in intron 8.

cells[1]. To date, more than 1969 sequence variations have been identified in the *CFTR* gene, including mutations that are involved in disease expression and polymorphisms which have no effect on the phenotype[2]. The rate of *CFTR* gene mutations varies greatly among different populations. Although the prevalence of CF in Iran is not known, current data suggest that the disease is not rare in this country. The most common mutation is ΔF508 with a frequency of 16% to 24% in different parts of Iran; these rates are much lower than in European countries[3].

The clinical presentations of CF varies widely from atypical mild disease to the classical form characterized by multiorgan involvement. The highly variable presentation depends on specific mutations, gene penetrance, the presence of genetic modifiers and environmental factors[4]. The diagnosis of classical CF is straightforward and based on specific clinical features, family history and positive sweat chloride tests, whereas the diagnosis of nonclassical CF is often delayed because of its unusual presentation or the late onset of symptoms. Delays in the diagnosis usually lead to progressive disease and even irreversible multiorgan damage[5]. The analysis of *CFTR* gene mutations is useful to better characterize the disease, especially when the results of sweat chloride tests are uncertain or variable. DNA-based testing is also useful for preconceptional screening, prenatal diagnosis for couples with a family history of CF, and preimplantation genetic diagnosis for couples with known *CFTR* genetic mutations who hope to have a healthy child by *in vitro* fertilization[5,6]. These tests are usually performed with a panel of known *CFTR* mutations for the ethnic group of interest. Sequencing the *CFTR* gene and multiplex ligation-dependent probe amplification (MLPA)-based testing are only done to diagnose rare or unknown variants[4].

CASE REPORT

A 16-year-old boy from Southwestern Iran with chronic productive cough and dyspnea was diagnosed as having CF in infancy based on typical findings of gastrointestinal and pulmonary manifestations with a positive sweat chloride test. He was the sixth child of healthy consanguineous parents and had two healthy older sisters and one healthy brother. The results of sweat chloride tests were normal for the parents and siblings, and none of them reported any symptoms or problems related with CF. Two of the patient's older brothers had died at the age of 6 mo; their medical history was unremarkable.

This patient had been hospitalized several times during infancy due to severe dehydration. He suffered from numerous recurrent pulmonary infections and greasy stools, which required frequent visits to his physician. Physical examination showed scattered bilateral coarse crackles, increased anteroposterior diameter of chest and digital clubbing.

At his most recent visit his bone age was estimated at about 12-year-old based on left-hand X-ray, and he also had symptoms compatible with delayed sexual maturation and delayed puberty. Laboratory parameters including blood cell count, fasting blood glucose, blood urea nitrogen, serum creatinine, calcium, phosphorus, erythrocyte sedimentation rate, C-reactive protein levels and liver function tests were normal at this visit, but his sweat chloride test results were higher than normal (> 100 mEq/L). Chest X-ray revealed bilateral infiltration and bronchiectasis in both lung fields. Abdominal and pelvic ultrasound examination disclosed no abnormal findings. Because of his abnormal heart sounds, echocardiography was performed which showed mild pulmonary artery hypertension. The patient was advised to continue treatment with antibiotics, chest physiotherapy, pancreatic enzyme replacement and vitamin supplementation.

An initial genetic study was done with the Elucigene CF29 v.2 kit (Tepnel, Oxfordshire, United Kingdom). Our patient lacked of both the normal and mutant forms of the fragment corresponding to the ΔF508 allele, whereas all his first-degree relatives carried the normal allele. This test was repeated three times with new blood samples, and the results were consistent across tests. Genetic analysis was then performed with the Elucigene CF-EU2 v.1 kit (Gen-Probe Life Science Ltd., Manchester, United Kingdom), which is designed to identify 50 mutations. This kit is also able to identify the number of TG repeats associated to the polythymidine tract at the junction of intron 8 and exon 9, which affects the splicing efficiency of exon 9 and influences the gene transcription rate. This analysis showed the absence of PCR amplification products for all fragments mapping to exons 4-10, suggesting that he was homozygous for a deletion spanning exons 4 to 10 of the *CFTR* gene (*CFTR* del 4-10), as a result of first-degree consanguinity between his parents. This homozygous deletion was confirmed by MLPA and was detected in the heterozygous state in both parents (Figure 1), in one of the sisters and in his brother. The 40-kb del 4-10 CF mutation was previously reported in compound heterozygous patterns in two patients with CF: an 8-year-old French girl with the ΔF508/

CF 40-kb del 4-10 genotype combination[7] and a 19-year-old Caucasian female with the c.1220del20/CF 40-kb del 4-10 genotype combination[8]. In contrast to the latter patient with a frameshift mutation in the *CFTR* gene because of a 40-kb deletion, in our patient we predict an in-frame deletion removing 373 amino acids based on our sequencing results.

In conclusion, although there is no evidence to prove the relationship between *CFTR* gene mutations and disease severity or response to therapy, determining *CFTR* gene mutations in patients and their family members would be helpful to prevent the occurrence of new cases, especially in populations in which consanguinity is common.

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COMMENTS

Case characteristics

A 16-year-old boy with chronic productive cough and dyspnea was diagnosed as having cystic fibrosis (CF) in infancy based on gastrointestinal and pulmonary manifestations with a positive sweat chloride test.

Clinical diagnosis

Hospitalization during infancy due to severe dehydration and recurrent pulmonary infections and greasy stools.

Differential diagnosis

Celiac disease, primary immunodeficiency disorders.

Laboratory diagnosis

Positive sweat chloride test and lack of both normal and mutant forms of the fragment corresponding to the ΔF508 allele in molecular analysis.

Imaging diagnosis

Left-hand X-ray: bone age about 12-year-old based on. Chest X-ray: bilateral infiltration and bronchiectasis in both lung fields. Echocardiography: mild pulmonary artery hypertension.

Treatment

Antibiotics therapy, chest physiotherapy, pancreatic enzyme replacement and vitamin supplementation.

Related reports

Homozygous 40-kb del 4-10 in cystic fibrosis transmembrane regulatory *(CFTR)* gene was detected in this patient by multiplex ligation-dependent probe amplification (MLPA).

Experiences and lessons

Determining *CFTR* gene mutations in CF patients and their family members would be helpful to prevent the occurrence of new cases, especially in populations in which consanguinity is common.

Term explanation

MLPA is a technique for detecting deletions or duplications of one or more parts of a gene.

Peer review

The manuscript reports a patient with homozygous exon 4-10 *CFTR* gene deletion mutation. Overall, this manuscript is well written and suitable as a case-report.

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CASE REPORT

Gastric conduit perforation

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Abstract

As patients with carcinoma of the esophagus live longer, complications associated with the use of a gastric conduit are increasing. Ulcers form in the gastric conduit in 6.6% to 19.4% of patients. There are a few reports of perforation of a gastric conduit in the English literature. Almost all of these were associated with serious complications. We report a patient who developed a tension pneumothorax consequent to spontaneous perforation of an ulcer in the gastric conduit 7 years after the index surgery in a patient with carcinoma of the gastroesophageal junction. He responded well to conservative management. Complications related to a gastric conduit can be because of multiple factors. Periodic endoscopic surveillance of gastric conduits should be considered as these are at a higher risk of ulcer formation than a normal stomach. Long term treatment with proton pump inhibitors may decrease complications. There are no guidelines for the treatment of a perforated gastric conduit ulcer and the management should be individualized.

Key words: Gastric conduit; Ulcer formation; Perforation; Carcinoma of the esophagus; Proton pump inhibitors

Core tip: We report a patient with a spontaneous perforation of an ulcer in the gastric conduit of a patient who had surgery for carcinoma of the gastroesophageal junction. He responded to conservative management with continuous decompression of the conduit with Ryle's tube aspiration, proton pump inhibitors and enteral nutrition through a feeding jejunostomy for 4 wk. Periodic endoscopic surveillance should be considered as gastric conduits are at a higher risk of ulcer formation than a normal stomach and management of a perforated gastric conduit ulcer should be individualized.

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INTRODUCTION

The stomach is preferred as the conduit after esophageal resection. Complications following gastric conduits are being reported more often as patients with carcinoma of the esophagus are living longer after resection. The incidence of an ulcer occurring in a gastric conduit is reported to be between 6.6% and 19.4%[1,2]. Perforation of a gastric conduit ulcer, although rare, may be catastrophic. The ulceration in a gastric conduit is often due to tumor recurrence. However, it may be due to other causes too. We report a patient with spontaneous perforation of a gastric conduit ulcer into the right pleural cavity that was successfully managed conservatively.

CASE REPORT

A 50-year-old man underwent a transhiatal esophagec-

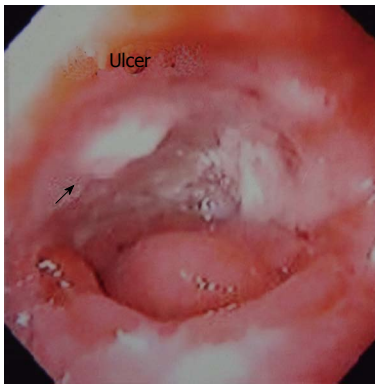

Figure 1 Endoscopic view of gastric conduit ulcer.

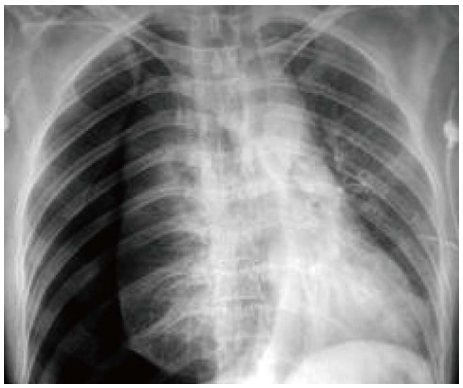

Figure 2 Chest X-ray showing right sided tension pneumothorax with mediastinal shift.

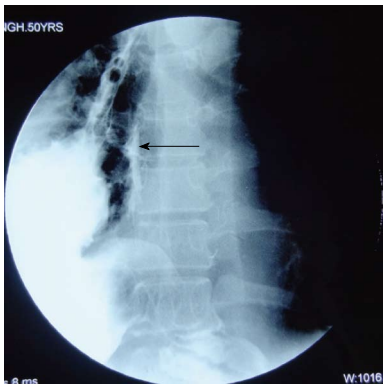

Figure 3 Oral Gastrografin study showing leak of contrast from the medial aspect of upper part of the conduit (arrow).

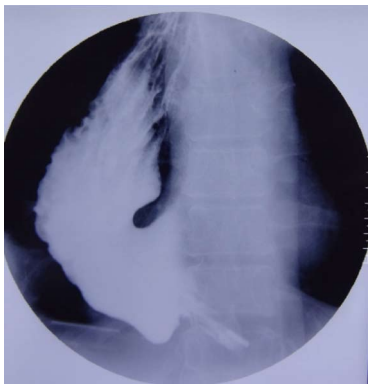

Figure 4 Repeat study after 4 wk shows no evidence of contrast leak.

tomy and stapled cervical esophagogastric anastomosis without pyloromyotomy for carcinoma of the gastroesophageal junction in 2005. He had a minor anastomotic leak in the immediate postoperative period which was managed conservatively. The histology revealed a well differentiated adenocarcinoma of the gastroesophageal junction, infiltrating the adventitia. The resected margins were free of tumor and metastasis was seen in one of six lymph nodes. He did not receive any adjuvant treatment. In January 2006 he presented with dysphagia. A barium swallow revealed a stricture at the anastomotic site and an endoscopic biopsy did not show any local recurrence. The stricture was dilated with Savary-Gilliard dilators (Wilson Cook) up to 14 mm in two sessions and the patient became euphagic. He remained asymptomatic until June 2012 when he started complaining of pain in the neck and epigastric region. Endoscopy showed a large ulcer in the gastric conduit just below the anastomotic site. A biopsy from the ulcer did not reveal any malignancy (Figure 1). He was started on proton pump inhibitors (PPI) and *Helicobacter pylori* (*H. pylori*) eradication therapy. In July 2012, he had sudden onset of difficulty breathing and pain in the right side of the chest. At the time of presentation to our hospital the patient was hemodynamically stable. His hemoglobin was 13 g/dL, total leukocyte count of 16000 per cumm, and the blood urea and serum creatinine was 45 mg/dL and 1.2 mg/dL, respectively. The chest X-ray showed a tension pneumothorax on the right side with mediastinal shift to the left (Figure 2). The week before the patient had taken non-steroidal anti-inflammatory drugs for pain. A liter of purulent fluid with gastric contents was drained from the right hemithorax after insertion of an intercostal drainage (ICD) tube and his respiratory distress subsided. An oral Gastrografin study revealed a leak from the proximal part of the gastric conduit into the right hemithorax (Figure 3). A feeding jejunostomy was done because of the poor nutritional status of the patient. He was managed conservatively with continuous decompression of the gastric conduit using a Ryle's tube (Romsins), antibiotics, PPIs, enteral nutrition through the feeding jejunostomy, serial chest X-rays and monitoring the ICD output. A follow up oral Gastrografin study at 4 wk revealed no evidence of any contrast leak from the gastric conduit (Figure 4). He was then allowed oral nutrition which he tolerated. There was no change in the nature and amount of the ICD fluid output. The ICD tube was subsequently removed and chest X-ray did not show any pleural effusion or pneumothorax. He is doing well with no symptoms at the 6 mo follow up. We did not manage this patient with insertion of an endoscopic stent as the leak was from the proximal part of the gastric conduit and the stent would have impinged on the cricopharynx. Stent migration was also likely because of the large diameter of the gastric

conduit.

DISCUSSION

Increasing use of the stomach as a conduit has led to increasing reports of peptic ulcers in the conduit. In a prospective study of annual endoscopic evaluations in 114 patients who underwent gastric tube reconstruction after esophagectomy, 47% of patients had secondary gastric tube diseases, including gastritis [35.1% (40/114)], benign gastric tumors [10.5% (12/114)], gastric ulcers [6.1% (7/114)] and gastric adenocarcinoma [3.5% (4/114)][1]. Gastric tubes are reported to be at a higher risk of developing an ulcer than the normal stomach. The cause of a gastric conduit ulcer remains controversial. Several mechanisms have been postulated for the formation of gastric conduit ulcers, including normalization of the intraluminal pH profile over time, *H. pylori* infection (especially in patients with a history of peptic ulcer before surgery), delayed gastric emptying as a result of vagal denervation, bile reflux, ischemia due to mobilization of the gastric conduit, radiation, use of non-absorbable sutures and intake of non-steroidal anti-inflammatory drugs (NSAIDs), aspirin or steroids[3]. Most ulcers develop within 20 cm of the esophagogastric anastomosis, as in our patient, because the microcirculation is most disturbed in the upper part of the conduit[2]. The time for development of these ulcers has varied widely, from one month to as long as 150 mo.

Peptic ulcer of the gastric conduit can present with anemia, retrosternal or epigastric pain, fullness after eating or dysphagia[3]. It could be asymptomatic and vagotomy may be one of the reasons for the absence of pain[4]. A gastric conduit ulcer often causes serious complications, such as bleeding and perforation[5]. It may penetrate into any adjacent organ (left ventricular or atrial wall, thoracic aorta and other major vessels) or cavity, including the right pleural cavity, bronchi and pericardial cavity[5].

Only a few cases of gastric conduit perforation have been reported in the English literature and almost all of them had serious complications. More than half the patients were treated conservatively and all of them died[5]. All patients whose conduit ulcer perforated into the tracheobronchial tree or cardiovascular system died. Only patients with perforation into the sternum and thoracic cavity survived. Patients who had a gastric conduit perforation in the thoracic cavity underwent either primary closure of the perforated ulcer or resection of the ulcer followed by an interrupted closure buttressed with a pleural patch. Both these procedures are associated with high leak rates and mortality. In our case, the patient responded to conservative treatment, although we cannot recommend this for all cases.

Endoscopic surveillance should be done at least once every 6 mo as gastric conduits are at a higher risk of ulcer formation than a normal stomach and many such ulcers tend to be asymptomatic. Successful healing of a gastric ulcer by PPIs has been reported[1]. This could prevent potentially lethal complications associated with it.

While complications in the gastric conduit are being reported increasingly, there are no guidelines for the treatment of a perforated gastric conduit ulcer. These patients are usually sick and may not tolerate major surgery. The conservative management protocol cited above resulted in a good outcome in our case, showing that surgery is not always required and the management should be individualized. Avoidance of analgesics and periodic surveillance of the conduit may prevent complications.

COMMENTS

Case characteristics

The patient presented with sudden onset chest pain and difficulty breathing.

Clinical diagnosis

On clinical examination, decreased breath sounds in the right hemithorax with hyper resonant note on percussion.

Differential diagnosis

Differential diagnoses were pneumothorax secondary to spontaneous rupture of pulmonary bullae, acute myocardial infarction and recurrence of disease.

Laboratory diagnosis

Laboratory investigations were inconclusive.

Imaging diagnosis

On imaging, chest X-ray revealed right sided tension pneumothorax with mediastinal shift to left, gastric contents on insertion of intercostal drainage tube and oral Gastrografin study showed leak from the gastric conduit.

Pathological diagnosis

Previous endoscopy showed a large ulcer in the proximal part of gastric conduit, biopsy was consistent with peptic ulcer and also ruled out any recurrence.

Treatment

He was treated conservatively with continuous decompression of the conduit through Ryle's tube aspiration, proton pump inhibitors and enteral nutrition through feeding jejunostomy for 4 wk.

Experiences and lessons

The possibility that ulceration in the gastric conduit may be due to causes other than tumor recurrence deserves greater recognition. Periodic endoscopic surveillance should be considered as gastric conduits are at a higher risk of ulcer formation than a normal stomach.

Peer review

This is a rare morbid complication of gastric conduit which responded to conservative management. However, a firm conclusion cannot be drawn on the management guidelines of perforated gastric conduit ulcer and treatment should be individualized.

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Format

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1 **Jung EM**, Clevert DA, Schreyer AG, Schmitt S, Rennert J, Kubale R, Feuerbach S, Jung F. Evaluation of quantitative contrast harmonic imaging to assess malignancy of liver tumors: A prospective controlled two-center study. *World J Gastroenterol* 2007; **13**: 6356-6364 [PMID: 18081224 DOI: 10.3748/wjg.13.6356]

Chinese journal article (list all authors and include the PMID where applicable)

2 **Lin GZ**, Wang XZ, Wang P, Lin J, Yang FD. Immunologic effect of Jianpi Yishen decoction in treatment of Pixu-diarrhoea. *Shijie Huaren Xiaohua Zazhi* 1999; **7**: 285-287

In press

3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

Both personal authors and an organization as author

5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

No author given

6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

Volume with supplement

7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

Issue with no volume

8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; (**401**): 230-238 [PMID: 12151900 DOI:10.1097/00003086-200208000-00026]

No volume or issue

9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

Books

Personal author(s)

10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

Chapter in a book (list all authors)

11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

Author(s) and editor(s)

12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

Conference proceedings

13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

Conference paper

14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

Electronic journal (list all authors)

15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/

ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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