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World Journal of Clinical Cases (*World J Clin Cases*, *WJCC*, online ISSN 2307-8960, DOI: 10.12998) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

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EDITORIAL

Important of case-reports/series, in rare diseases: Using neuroendocrine tumors as an example

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Core tip: A review of neuroendocrine tumors, which are rare diseases, strongly supports the prominent role and value of reporting of rare cases or small case series in uncommon disorders.

Nakamura T, Igarashi H, Ito T, Jensen RT. Important of case-reports/series, in rare diseases: Using neuroendocrine tumors as an example. *World J Clin Cases* 2014; 2(11): 608-613 Available from: URL: http://www.wjgnet.com/2307-8960/full/v2/i11/608.htm DOI: http://dx.doi.org/10.12998/wjcc.v2.i11.608

Abstract

At present the publishing of case reports or case series involving small numbers of cases is controversial. While in the past they were commonly published by most journals, recently a number of prominent journals have either stopped publishing them or markedly reduced the numbers published. However, recently an increasing case is being made for their value and a number of new journals have been started devoted specifically to their publication. One of the arguments used for their value is their prominent role in rare diseases either in their recognition, full description or development of treatments. However this aspect has not been specifically studied. In this editorial this aspect is specifically examined using their role in neuroendocrine tumors as an example. Furthermore, the background of the controversy is briefly reviewed to better understand the context of this editorial.

Case reports (1 patient) or case series (> 1 patient) reporting are not without controversy: held in high regard by some[1-4] and looked down on by others as occupying the lowest rung in the evidence pyramid hierarchy[5-10]. It is necessary to understand a little more of this controversy to understand why this editorial is being written, which will be covered briefly in the next paragraph. The purpose of this editorial is to demonstrate, how in the case of an uncommon disease, such as clinically important gastrointestinal (GI) neuroendocrine tumors [carcinoids (incidence-7-13 cases/million per year) and pancreatic neuroendocrine tumors (pNETs) (incidence-1-5 cases/million per year)][11,12], case reports and case series reports have played, and are still playing, a vital and essential role in their recognition and also management/treatment.

Case or case series reports are controversial because an increasing number of prominent journals, starting in the 1980's no longer regularly published them[9,13,14]. In a survey in 1979[15] of three prominent medical journals (NEJM, JAMA, Lancet) of articles published between 1946-1974, the frequency of case reports/series (< 10 patients) remained unchanged, at 38% of all articles.

However, analyzing the same journals from 1971-1991[14], found that case reports/series frequency, as a percentage of all articles, decreased 86% from 30% to 4% of all articles, replaced by an increase in primarily clinical trials and other evidence based medicine (EBM) reports [randomized clinical trials (RCT), *etc.*]. In another study in 2006[16] of 25 journals covering various aspect of medicine, only 32% regularly published case reports/series and 33% never published them. Furthermore, other publications including areas as diverse as psychiatry and anesthesia, found that journals prominent in their field, either stopping reporting case reports/series or only infrequently published them[5,9,10,13]. This change in policy is generally attributed primarily to two factors: a general conclusion that case reports/series represent a lower level of evidence [compared to randomized clinical trials (RCT), systematic reviews, meta-analyses, cohort studies, case control studies][6,10] and the rise of the importance of impact factors (IF)[6,10].

In general case reports/series are ranked as providing one of the lowest levels (Level 3) in the evidence based hierarchy[2,6,9,10]. They have a denominator of only one (or a small number); the results can not be used for predictive value, and they can be notoriously affected by publication bias[6,10,17,18]. For example, one study[17] demonstrated in a review of case reports/series, successes were reported in 90% and failures in only 10%. It has been stated that nearly all discarded once-popular therapies were likely supported by a series of favorable cases[18]. Over the last few years, the impact factor of journals (which is determined by the citation rate) is assuming increasing importance. This is occurring because, not only is it widely used as a measure of a journal's quality, which can not only have an economic influence on the journal and the quality of the papers submitted, but also have an affect on authors, because it is increasingly used in assessing an individual's academic credentials in terms of assessing quality of publications for possible placement, promotion or other advancement[6,9,10]. The problem here is that case reports/series are generally cited less than evidence-based medicine (EBM) articles with the result they can decrease the IF of the journal[2,6,8-10,19]. This is well shown in a 2005 study[8] comparing the impact factor of various types of articles (2646 articles published in 1991, 2001). This study[8] showed case reports were the most poorly cited compared to EBM studies (meta-analysis, RCTs, epidemiological studies, case control studies). Similar results were found in a study assessing the citation rate in 2008 of papers published in *Am J Medical Genetics*, Part A in 2006, which found that the non-citation rate was 2.3 fold higher in the case reports/series than in EBM articles, and the citation rate in the case reports/series was not > 6 citations for any article, whereas in the EBM articles, many had rates higher than this.

While the presence of these negative factors discussed above, might be assumed to be leaving the case report/series in its terminal throes, in the last few years an increasing argument in their defense has been made by many[1-3,6,7,17,19-21] and for its restoration, as a prominent and useful medical reporting method. This is evidenced by both the recent appearance of numerous publications devoted to case reports/series such as the *World J of Clinical Cases*, as well as the re-institution of the case report/series format in some prominent journals[19,20,22]. One study[17] assessed one aspect of the re-inclusion of case reports into the journal Lancet[20] by studying the impact of case reports/series of innovative treatments reported in 1995/1996. This approach was taken because it is recognized that for a clinical study to be funded, evidence must be provide that proposed treatments may have merit, and case reports/series are often the first line of such evidence[17]. Of the 64 cases reports and 39 case series identified, it was found the cases were clearly read because they had an average citation rate of 17 times (range 0-336), and they also affect subsequent approaches because 22% of the cases lead to followup trials (9%-controlled trials)[17]. Other important points raised in their defense include that case reports/series: have a long tradition in teaching in medicine; they often report and establish the cause of various disorders with few observations; they provide the clinical foundation for postulating the possible pathogenesis of disorders; for therapies they are often the first evidence of the effectiveness of a new therapy, as well as often the major source of initially reporting adverse effects of different therapies; are an important teaching, education and career vehicle for young physicians (students, residents, fellows, starting faculty) to publish and contribute to the medical literature; and are important in recognizing new diseases, particularly in the case of rare diseases or rare variations of more common diseases[2,6,10,17,19,21-23]. While numerous articles have mentioned the importance of case reports/series reporting in rare diseases, this point has not been specifically examined and emphasized. It occurred to us that the study of GI-NETs (carcinoids, pNETs) offers a very good example of this assertion and thus will be briefly reviewed here and in Table 1.

Both GI- carcinoids and pNETs are classified as neuroendocrine tumors (NETs)[24-26] and although they have a different pathogenesis, they share similar histological features, aspects of their biological behavior, and many features of their management including localization methods, treatment approaches, and their abilities to be associated with hormonal-excess states due to ectopic production of biologically active substances[24,25,27-29]. There are 10 well-established pNET syndromes of which 9 are associated with specific hormone excess syndromes [Gastrinomas; insulinomas; VIPomas; glucagonomas; somatostatinomas; GRFomas; pancreatic ACTHomas; pNETs causing carcinoid syndrome, or hypercalcemia and nonfunctional pNETs (NF-pNETs)][11,26]. In addition to these 10 established pNET syndromes there are 5 other very rare (< 5 cases reported) syndromes associated with pNETs[26], which also likely represent a functional pNET syndrome. These include: pNETs secreting erythropoietin causing erythroblastosis[30]; pNETs secreting

Table 1 Sentinel case reports/series defining syndromes of disease aspects in patients with gastrointestinal neuroendocrine tumors

Year	Author	Pt#	Type of report	Syndrome	Importance	Ref.
1890	Ranson	1	Case report	Carcinoid	First description of ileal carcinoid	[50]
1902	Nichols	1	Case report	Insulinoma	First islet tumor	[49]
1922	Banting *et al*	7	Case report	Insulin treatment diabetes	Extracted insulin and effectiveness of insulin therapy in diabetes mellitus demonstrated.	[51]
1924	Harris *et al*	3	Case report	Insulinoma	1st postulate the possibility of insulinoma in his patients	[37]
1927	Wilder *et al*	1	Case report	Insulinoma	1st pNET syndrome (insulinoma). Extracting insulin from malignant pNET operated by WJ Mayo	[62]
1938	Whipple	Case review	Case review	Insulinoma	Diagnostic triad for insulinoma proposed	[52]
1942	Becker *et al*	2	Case report	Glucagonoma	First description of Glucagonoma in a patient with skin rash later found to have pNET	[38]
1950	Del Castillo *et al*	1	Case report	Cushing syndrome	First pNET associated with Cushing syndrome	[39]
1954	Thorson *et al*	16	Case series review	Carcinoid syndrome	First described a series of patients with small intestinal carcinoids, establishing the clinical entity "carcinoid syndrome"	[48]
1955	Zollinger *et al*	2	Case report	ZES	First description of ZES (gastrinoma)	[40]
1957	Priest *et al*	1	Case report	VIPoma	Recognition of WDHA syndrome (VIPoma) with pNET	[41]
1958	Verner *et al*	2	Case report	VIPoma	First complete description of all features WDHA from review/2 personal cases and 7 literature cases	[63]
1966	McGavran *et al*	1	Case report	Glucagonoma	Reported case of pNET with hyperglucagonemia and glucose elevation	[54]
1971,3	Wilkinson	1	Case report	Glucagonoma	Proposed term "NME" to describe rash in glucagonoma.	[55,56]
1974	Mallinson *et al*	9	Case series review	Glucagonoma	Reviewed pNET secreting glucagon and called attention to their association with necrotic migratory erythema (NME)	[57]
1977	Larsson *et al*	2	Case report	Somatostatinoma	Initial case of pNET producing somatostatin with symptoms	[42]
1977	Ganda *et al*	1	Case report	Somatostatinoma	Initial case of pNET producing somatostatin with diabetes	[43]
1978	Caplan *et al*	1	Case report	GRFoma	1st case of pNET secreting growth hormone-like substance with acromegaly	[46]
1979	Krejs *et al*	1	Case report	Somatostatinoma	Clinical features of somatostatinoma syndrome described and full endocrine characterization	[44]
1982	Guillemin *et al*	1	Biochemistry	GRFoma	Isolation of growth-hormone releasing factor (GRF) from patient with acromegaly with pNET	[45]
1982	Rivier *et al*	1	Case report	GRFoma		[64]
1982	Ruddy *et al*	1	Case report	Reninoma	First description of renin secreting pancreatic tumor causing symptoms	[31]
2004	Samyn *et al*	1	Case report	EPOma	Description of pNET secreting erythropoietin with syndrome	[30]
2004	Brignardello *et al*	1	Case report	LHoma	Description of pNET secreting luteinizing hormone with syndrome	[35]
2008	Chung *et al*	1	Case report	IGF-2oma	First report of pNET secreting IGF-2 with symptoms	[33]
2012	Roberts *et al*	1	Case report	GLP-1oma	First description of pNET secreting GLP-1 causing symptoms	[32]
2013	Rehfeld *et al*	1	Case report	CCKoma	First description of CCK secreting pNET with syndrome	[47]

CCKoma: pNET secreting cholecystokinin; EPoma: pNET secreting erythropoietin; GRFoma: pNET secreting Growth Hormone Releasing Factor; IGF-1oma/IGF-2oma: pNET secreting insulin-like growth factor 1 or 2; LHoma: pNET secreting luteinizing hormone; NET: Neuroendocrine tumor: NME: Necrolytic migratory erythema (skin rash) seen in glucagonoma cases; pNET: Pancreatic neuroendocrine tumor; Reninoma: pNET secreting renin; Somatostatinoma: pNET secreting somatostatin; VIPoma: pNET secreting vasoactive intestinal peptide; WDHA: Watery diarrhea, hypokalemia and achlorhydria which are features seen in VIPoma patients; ZES: Zollinger-Ellison syndrome due to ectopic secretion of gastrin by a gastrinoma causing acid hypersecretion.

renin causing hypertension[31]; pNETs secreting GLP-1 or GLP-2 causing hypoglycemia[32,33] and pNETs secreting luteinizing hormone causing masculinization[34,35]. Although the incidence of both carcinoid tumors and pNETs is increasing, they are still classified as rare conditions[36]. Whereas gastrinoma, insulinoma and NF-pNETs are the most frequent pNETs, they still have an incidence < 2/million per year and are thus rare diseases (less 1 in 1500), whereas the other pNET syndromes are 1/10-1/100 less frequent[11,12,26,29]. The functional syndrome seen most frequently with GI-carcinoid tumors is the carcinoid syndrome, characterized by flushing, diarrhea, asthma and heart disease primarily due to ectopic release of serotonin, neurokinins and perhaps other biologically active peptides[29]. The carcinoid syndrome occurs in 5%-10% of patients with carcinoid tumors and thus is also present at < 3-5/million per year and hence is also a rare disease.

As can be seen in Table 1, case reports or case series, often involving < 5 cases, played a sentinel role in most GI-NET/pNET syndromes, usually providing the initial description of the functional syndrome or in

elucidation its full clinical manifestations. Specifically, case reports/series provided the initial description of insulinoma[37], glucagonoma[38], pNETs causing ectopic Cushing's syndrome[39], gastrinoma causing the Zollinger-Ellison syndrome[40], the VIPoma (WDHA) syndrome[41], somatostatinoma and somatostatinoma syndrome[42-44], GRFoma[45,46], pNETs secreting renin[31], pNETs secreting erythropoietin[30], pNETs secreting luteinizing hormone[35], pNET secreting IGF-2 (IGF-2oma)[33], pNETs seeing IGF-1(IGF-1oma)[32], and CCKoma[47]. The initial description of the carcinoid syndrome, seen in patients with metastatic carcinoid tumors to the liver (usually ileal-jejunal-midgut tumors) was described also in a case series[48]. The sentinel role of some case reports was recognized by naming the syndrome after the initial case description such as the Verner Morrison syndrome (VIPoma-WDHA) and the Zollinger-Ellison syndrome (gastrinoma). Some of the case reports/series played other sentinel roles. These include the first description of a pNET in a report of one patient[49]; the first description of an ileal carcinoid in one case[50]; the initial use of insulin for diabetes in a case series by Banting[51] and the initial description of the clinical triad that is commonly used, even today, to suspect the diagnosis of insulinoma[26,28,52] was in a case series review, and is now referred to as Whipple's triad after this sentinel paper[53]. Some case reports/series were not the first to report a new syndrome, but played an important role in defining the spectrum of the syndrome by describing additional features of the rare pNET syndrome. This is illustrated by case reports describing the full features of the VIPoma syndrome (diarrhea, hypokalemia, achlorhydria, hypercalcemia, not associated with peptic ulcer disease or gastric hypersecretion)[11,26], after the initial report of a nonbeta cell islet tumor (pNET) associated with large volume diarrhea causing hypokalemia[41]. Similarly additional case reports/case series after the initial description of the glucagonoma syndrome (pNET with skin rash)[38], described the association of a pNET with hyperglycemia and hyperglucagonemia[54], and emphasized its association with a characteristic skin rash, which was named necrolytic migratory erythema (NME)[55-57], and which was sufficiently distinctive to become one of the main features leading to the diagnosis of glucagonomas, even at present[11,26,28,58]. Lastly, this is also the case with the somatostatinoma syndrome which was first proposed in 1977 with the description of a somatostatin secreting pNET[42], whereas the full clinical features we generally recognize today [diabetes mellitus, cholelithiasis, steatorrhea, weight loss hypo/achlorhydria, anemia][11,26,58], were later described in another case report[44]. This latter finding, illustrates another important role of case reports/case series not only in rare disorders, but also in common disorders[2,3,10,19,21,59], by reporting an uncommon feature of a common disorder or, in our case, an additional feature of a previously described, uncommon disorder.

Another conclusion that can be drawn from the findings in pNETs illustrated in Table 1 is that case reports/series have had a prominent role in GI-NETs for longer than one century, and are still playing a prominent role. This is illustrated by the descriptions of numerous new pNET functional syndromes since 2000 (Table 1) with the most recent being a case report of a patient with a cholecystokinin secreting tumor syndrome (CCKoma)[47]. The CCKoma syndrome clinically included diarrhea, severe weight loss, advanced peptic ulcer disease, cholelithiasis, all of which can be explained by the known actions of CCK expected from the profound hyperCCKemia this patient had (1000-fold increased)[47]. At present it remains unknown whether this is a very rare syndrome, which has long evaded description, or whether it is more frequent and might be responsible for patients presenting with ZES-like feature, but with normal serum gastrin levels[47,60,61].

In conclusion, a review of the role of case reports/case series in the description and establishment of the GI-NET syndromes strongly support their importance in this rare group of diseases and supports the proposal that they can play a particularly important role in any rare disease[2,6,10,17,19,21-23]. The use of case reports/case series has not only provided many of the original descriptions of these rare GI-NET syndromes, they have provided other features leading to treatments as well as full characterization of aspects of the syndromes. Case reports/small series have been important throughout the last century in the elucidation of these rare syndromes and are as important today, as they were in the past.

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REVIEW

Evolution of endovascular mechanical thrombectomy for acute ischemic stroke

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Abstract

Acute ischemic stroke (AIS) is a common medical problem associated with significant morbidity and mortality worldwide. A small proportion of AIS patients meet eligibility criteria for intravenous thrombolysis (IVT) with recombinant tissue plasminogen activator, and its efficacy for large vessel occlusion is poor. Therefore, an increasing number of patients with AIS are being treated with endovascular mechanical thrombectomy when IVT is ineffective or contraindicated. Rapid advancement in catheter-based and endovascular device technology has led to significant improvements in rates of cerebral reperfusion with these devices. Stentrievers and modern aspiration catheters have now surpassed earlier generation devices in the degree and rapidity of revascularization. This progress has been achieved with no concurrent increase in risk of major complications or mortality, both when used alone or in combination with IVT. The initial randomized controlled trials comparing endovascular therapy to IVT for AIS failed to show superior outcomes with endovascular treatment, but key limitations of each trial may limit the significance of these results to current practice. While endovascular devices and operator experience continue to evolve, we are optimistic that this will be accompanied by improvements in patient outcomes. This review highlights the major endovascular devices used in current practice and the trials which have investigated their efficacy.

Key words: Cerebral infarction; Endovascular procedures; Intracranial hemorrhages; Stents; Stroke

Core tip: This review discusses the critical advancements in endovascular device technology for the treatment of acute ischemic stroke. Endovascular mechanical thrombectomy is becoming an increasingly utilized treatment approach for patients in whom intravenous thrombolysis with recombinant tissue plasminogen activator is ineffective or contraindicated. While three recent randomized controlled trials found no benefit of endovascular thrombectomy over intravenous therapy, it is important for clinicians to understand the limitations of these trials and recognize the expected key role of endovascular therapy in the future management of stroke patients.

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INTRODUCTION

The annual incidence of stroke in the United States is approximately 795000[1]. Stroke is the second leading cause of lost disability-adjusted life-years in high-income

Table 1 Summary of endovascular mechanical thrombectomy devices

Device	Manufacturer	Mechanism
Merci retriever	Concentric Medical	Thrombus retrieved with helical snare
Penumbra system	Penumbra Inc.	Thromboaspiration
Solitaire FR	eV3 Endovascular	Thrombus incorporated into struts of deployed stent
Trevo Pro	Stryker neurovascular	Thrombus incorporated into struts of deployed stent

countries and the second most common cause of mortality worldwide[2,3]. Approximately 80% of strokes are ischemic and 20% are hemorrhagic[4]. Acute ischemic stroke (AIS) is caused by a focal interruption of cerebral blood flow, most commonly due to occlusion of a major cerebral artery by local thrombosis or embolus. The resulting ischemia leads to tissue damage through a complex pathophysiological response of excitotoxicity, peri-infarction depolarization, inflammation and apoptosis[5].

The goal of therapy for AIS is to achieve cerebral reperfusion before neurological damage becomes irreversible. The correlation between vessel recanalization and favorable neurological outcome is well-studied[6,7], although additional factors such as stroke severity and age are also likely to have a significant impact on clinical outcome[8,9]. Currently, the only FDA-approved treatment with level 1 evidence for AIS is intravenous thrombolysis (IVT) with recombinant tissue plasminogen activator (alteplase) within three hours of symptom onset[10]. Additional trials have demonstrated that extending this time window to 4.5 h is beneficial in appropriately selected patients[11,12]. However, few patients (< 10%) meet eligibility criteria for this therapy[13-15]. Additionally, larger and more proximally-located thrombi may be relatively resistant to IVT[16-21]. Successful recanalization of large vessel occlusion (LVO) with IVT alone is infrequent, ranging from 10% in internal carotid artery (ICA) occlusions to 30% in middle cerebral artery occlusions, and IVT is associated with a risk of systemic and intracerebral hemorrhage (ICH)[22].

These limitations have led to the exploration of alternative or complementary treatment approaches for AIS. Endovascular mechanical thrombectomy has developed over the past decade as a safe and effective intervention. Rapid advancement in catheter-based and endovascular device technology has led to an increasing number of patients with AIS being treated when IVT is ineffective or contraindicated[14]. Here, we review the evolution of endovascular mechanical thrombectomy devices for the treatment of AIS.

ENDOVASCULAR MECHANICAL THROMBECTOMY

Endovascular treatment of AIS began with intra-arterial (IA) infusion of thrombolytic agents. Several studies investigating these therapies reported favorable rates of vessel recanalization and neurological outcomes[23-25]. Given the relatively favorable risk to benefit profiles of current mechanical thrombectomy devices, IA thrombolysis is infrequently used in modern endovascular AIS therapy. This was followed by the implementation of balloon angioplasty and microwire techniques to mechanically disrupt thromboemboli[26,27]. Additionally, intracranial stents were shown to be effective at restoring blood flow when deployed within an occluded vessel[28,29].

Endovascular retrieval devices were first developed to recover errant coils and other foreign bodies that had embolized within the cerebral circulation during endovascular procedures[30-32]. The development of devices to remove occlusive thromboemboli was thus a natural extension of pre-existing technology. Endovascular mechanical thrombectomy involves physical extraction of the thrombus through a catheter. Due to the anatomical limitations imposed by vascular anatomy on currently available thrombectomy catheters, thrombi in large ICA, the Circle of Willis and the first two branches of the anterior (A1 and A2), middle (M1 and M2) and posterior (P1 and P2) cerebral arteries) are the most readily accessible. Smaller branches of the cerebral circulation are often too narrow and tortuous to undergo successful mechanical thrombectomy.

Alternative treatment methods for strokes from LVO are an important development, as medical management is often unsuccessful, and these strokes are associated with high rates of morbidity and mortality[25]. The two main methods of endovascular mechanical thrombectomy for LVO include: (1) physical grasping and removal of thrombi with retrieval devices and (2) aspiration of occlusive thrombi with suction devices (Table 1).

MERCI RETRIEVER

The Merci Retriever (Concentric Medical, Mountainview, CA) was FDA-approved in August 2004 as the first clot retriever device in the United States. This device utilizes memory shaped nitinol (nickel titanium) material to convert from a straight to helical configuration to grasp the thrombus. In this procedure[33]: (1) the retriever is advanced through the thrombus in its straight configuration; (2) two to three helical loops are deployed beyond the thrombus; (3) the device is retracted to contact the thrombus, and proximal loops are deployed within the thrombus; (4) a balloon guide catheter located in the common or internal carotid artery is inflated to control intracranial blood flow; and (5) three to five clockwise rotations are performed to fully ensnare the thrombus, and the Merci Retriever-thrombus complex and microcatheter are removed together.

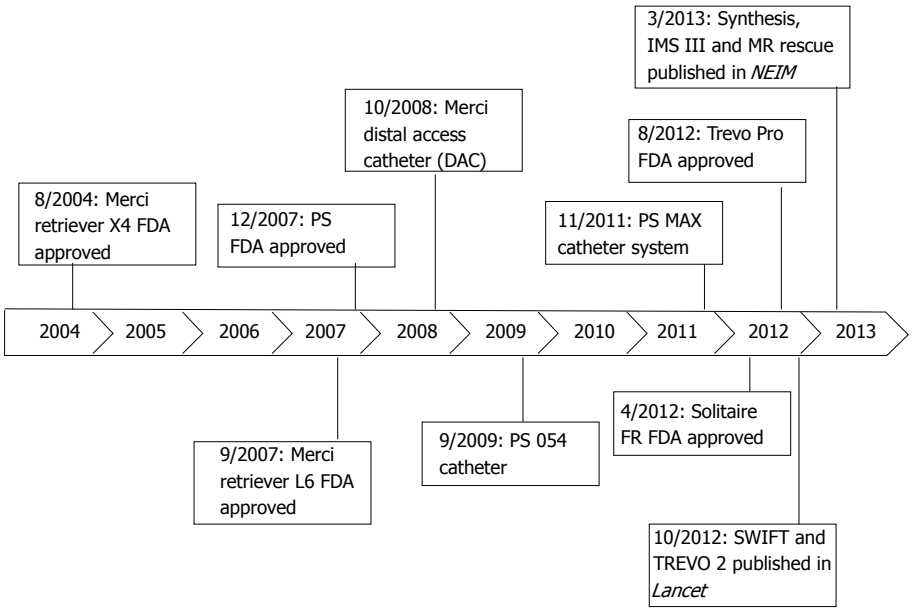

Figure 1 Timeline of FDA approval, release dates and randomized controlled trials of endovascular mechanical thrombectomy devices.

The Mechanical Embolus Removal in Cerebral Ischemia (MERCI) trial was a prospective, non-randomized, multicenter trial that first evaluated this device[34]. Recanalization, defined as Thrombolysis in Myocardial Infarction (TIMI) grade 2 or 3 flow in all treatable vessels, was achieved in 48% (68/141) of patients. Patients with recanalization had better neurological outcomes ($P < 0.0001$), as determined by modified Rankin Score (mRS) of 2 or less at 90 d, and lower mortality rates ($P = 0.01$) than those without recanalization, and procedure-related complication and symptomatic ICH rates were comparable to trials of IV t-PA, combined IV/intra-arterial t-PA, and intra-arterial prourokinase[10,25,35].

Newer device generations (Figure 1) have moderately improved rates of recanalization[36]. One such advancement was the Distal Access Catheter (DAC; Concentric Medical) in 2008. The DAC has a flexible distal shaft that facilitates its navigation around the anterior genu of the ICA, beyond the origin of the ophthalmic artery[37]. This improved the navigation of the Merci Retriever through the carotid siphon with each pass, improving procedural efficiency.

PENUMBRA SYSTEM

The Penumbra System (PS) (Penumbra Inc., Alameda, CA) was FDA-approved in December 2007 and utilizes aspiration for thrombus extraction. In this procedure[38]: (1) the PS catheter is advanced through a guide catheter to a point just proximal to the occlusion; (2) a microwire called a separator is repeatedly passed through the thrombus in order to fragment the clot; and (3) constant suction is applied to the PS catheter to aspirate the thrombus fragments.

The PS was evaluated in a prospective, multicenter study of 125 patients with National Institute of Health Stroke Scale (NIHSS) score $\geqslant 8$ who were ineligible for or refractory to IVT[38]. Recanalization (TIMI $\geqslant 2$) was achieved in a high proportion (81.6%) of patients without significantly different complication rates than those seen in the MERCI trials. Good clinical outcome (mRS $\leqslant 2$) was observed in 25% of patients at 30-d follow-up. More recent generations of the PS include the 054 Reperfusion catheter (2009) and the MAX Reperfusion catheter line (2011). These devices achieve greater aspiration force due to larger proximal lumens[39]. The 054 Reperfusion device was found to accomplish recanalization at a median time of 20 min[40], significantly less than the median time of 45 min reported in the penumbra pivotal trial using previous generation technology.

STENTRIEVER DEVICES

Stentrievers utilize a retrievable stent to engage and remove the thrombus. In this procedure[41]: (1) the stentriever is advanced within a microcatheter through the thrombus until it is a few millimeters distal to the clot; (2) the stent is deployed, incorporating the thrombus into the stent struts and displacing it radially to the vascular wall; and (3) after three to five minutes, the microcatheter and stentriever are removed together under continuous proximal aspiration with a syringe. This must be performed cautiously, as at least one case of intracranial extravasation during device withdrawal has been reported[42]. It is also possible to perform a control angiogram while the stentriever is deployed, which can confirm flow restoration. However, since this may promote distal migration of thrombus fragments, the utility of performing an angiogram during stentriever deployment is controversial.

Solitaire FR

The Solitaire FR (eV3 Endovascular, Irvine, CA) was

Table 2 Comparison of randomized trials of endovascular thrombectomy for AIS

Trial	Treatment arms	*n*	Revascularization[a] (%)	Good outcome[bc] (%)	Symptomati[c] ICH (%)	Mortality[b] (%)
SWIFT	Merci Retriever	55	67	33	11	38
	Solitaire FR	58	89	58	2	17
TREVO 2	Merci Retriever	90	60	22	2	24
	Trevo Pro	88	86	40	4	33
SYNTHESIS[d]	IVT	181	NR	35	6	6
	EVT	181	NR	30	6	8
IMS III	IVT	222	NR	39	6	22
	IVT + EVT	434	[e]	41	6	19
MR Rescue	Penumbral, IVT	34	93	26	6	21
	Penumbral, EVT	34	67	21	9	18
	Nonpenumbral, IVT	20	78	10	0	30
	Nonpenumbral, EVT	30	77	17	0	20

[a]Defined as TIMI or TICI grade ⩾ 2a, final revascularization rate including rescue therapies; [b]Assessed at 90 d unless otherwise specified; [c]Defined as mRS ⩽ 2 unless otherwise specified; [d]This study used mRS ⩽ 1 as the primary clinical efficacy endpoint and assessed mortality at day 7 ± 2; [e]Reported as 65%, 81%, 70% and 77% for ICA, M1, single M2 and multiple M2 occlusions, respectively; statistically significant ($P < 0.05$); SWIFT: SOLITAIRE™ with the intention for thrombectomy; TREVO 2: Thrombectomy REvascularization of Large Vessel Occlusions in Acute Ischemic Stroke; AIS: Acute ischemic stroke; IMS: Interventional Management of Stroke; IVT: Intravenous thrombolysis; ICH: Intracerebral hemorrhage; TIMI: Thrombolysis in Myocardial Infarction; TICI: Thrombolysis in Cerebral Ischemia; mRS: Modified Rankin Score.

approved by the FDA in March 2012. Initial non-randomized case series with the Solitaire FR demonstrated high rates of recanalization (89%-96%) and improved rates of favorable clinical outcome (mRS ⩽ 2; 42%-69%) compared to earlier devices[29,41,43-45]. The Solitaire FR was then directly compared to the Merci Retriever in the SOLITAIRE™ with the intention for thrombectomy (SWIFT) trial (Table 2)[46]. This was a parallel-group, non-inferiority trial of 113 patients randomized to either the Solitaire (n = 58) or Merci (n = 55) device. The primary outcome (TIMI ⩾ 2) was more likely to be achieved in the Solitaire group than the Merci group (64% *vs* 24%; $P < 0.0001$ non-inferiority; $P = 0.0001$ superiority). Additionally, patients in the Solitaire group were more likely to achieve a good neurological outcome (mRS ⩽ 2) at 90 d (58% *vs* 33%; $P < 0.0001$ non-inferiority; $P = 0.02$ superiority) and had a lower 90-d mortality rate (17% *vs* 38%; $P = 0.0001$ non-inferiority; $P = 0.02$ superiority) than those in the Merci group. Subsequent prospective and retrospective studies have continued to demonstrate high rates of vessel recanalization and good clinical outcomes with the Solitaire FR[47,48].

Trevo Pro

The Trevo Pro (Stryker Neurovascular, Kalamazoo, MI) is another retrievable stent system which was approved by the FDA in August 2012. Similar to the Solitaire FR, the Trevo Pro was found to be superior to the Merci Retriever in a head-to-head randomized study[49]. The Thrombectomy REvascularization of Large Vessel Occlusions in Acute Ischemic Stroke trial assigned patients with AIS from LVO to either the Trevo Pro (n = 88) or Merci Retriever (n = 90) device. Patients in the Trevo Pro group were significantly more likely to reach the primary outcome, defined as Thrombolysis in Cerebral Ischemia (TICI) grade ⩾ 2, (86% *vs* 60%; $P < 0.0001$ superiority) and achieve a good 90-d neurological outcome (mRS ⩽ 2; $P = 0.013$) than those in the Merci Retriever group. No significant difference was observed in the safety profile (a composite of symptomatic ICH and procedure-related complications; $P = 0.1826$) or 90-d mortality rates ($P = 0.1845$) of these two devices.

A review of 13 prospective trials endorsed improved rates of vessel recanalization with the newer generation stentriever devices[50]. While early trials (mainly utilizing IA thrombolysis and the Merci Retriever) reported recanalization rates of approximately 50%, recent trials with stentrievers consistently reported rates of approximately 85%. A significantly greater time from symptom onset to endovascular treatment in more recent trials was also observed. This may explain their finding that although vessel recanalization rates have significantly improved over time, functional outcomes remain relatively stagnant. Nevertheless, stentrievers and large bore aspiration catheters have become the dominant endovascular devices used to treat AIS in modern practice. A recent prospective trial found no major differences in the efficacy or safety of the Solitaire FR and Trevo Pro[51].

COMBINED SUCTION EMBOLECTOMY AND MECHANICAL RETRIEVAL

The MAX reperfusion catheters allowed for the development of direct aspiration as an additional thrombectomy technique. Direct suction can be applied from the PS device or a syringe plunger connected to the proximal hub of the catheter. Previously, this technique was limited by the challenges of tracking an aspiration catheter through the intracranial circulation, but the improved trackability of the MAX reperfusion catheters has facilitated its development[37]. Furthermore, these catheters can still be used in combination with other endovascular devices. The ADAPT technique[52] is an increasingly utilized ap-

proach which combines modern aspiration and retrieval technology. Direct aspiration with a large bore aspiration catheter (commonly MAX reperfusion system) is first performed. If direct aspiration fails, stentrievers, balloons and stents can be still be passed through the catheter. A recent retrospective series of 98 patients by Turk *et al*[53] reported revascularization (TICI ⩾ 2b) in 78% of cases following direct aspiration. When stentrievers were used following failed direct aspiration, this rate rose to 95%, a previously unparalleled result.

Penumbra 3D separator

The Penumbra 3D Separator is the newest generation PS device currently being investigated in randomized controlled trials. It is designed to combine stentriever and direct aspiration technology into a single device. The new separator device is configured similarly to a stentriever, with an additional radial dimension to fragment the clot under continuous direct aspiration. The stent struts are designed to minimize vessel contact and thus theoretically reduce iatrogenic injury to the endothelium. An initial prospective study of 20 patients treated with the Penumbra 3D Separator demonstrated vessel recanalization (TICI ⩾ 2b) and favorable neurological outcome (mRS ⩽ 2) in 85% and 50% of patients, respectively[54].

ENDOVASCULAR THERAPY *VS* IVT FOR AIS

Due to the promising results from early pilot trials of endovascular mechanical thrombectomy for AIS[55,56], randomized controlled trials were undertaken to evaluate the benefit of endovascular therapy compared to IVT in a more rigorous fashion.

IMS III

The Interventional Management of Stroke (IMS) Ⅲ trial[57] randomly assigned 656 patients who had received IVT within three hours of AIS symptom onset to receive additional endovascular therapy (n = 434) or IVT alone (n = 222) in a 2:1 ratio. In the endovascular group, 330 patients received treatment: IA thrombolysis alone (n = 160), mechanical thrombectomy alone (n = 57), IA thrombolysis plus mechanical thrombectomy (n = 97) and combinations of multiple mechanical thrombectomy devices with or without IA thrombolysis (n = 16). There was no significant difference between the endovascular and IVT groups for achieving a 90-d mRS ⩽ 2 (40.8% and 38.7%, respectively; 95%CI: -6.1 to 9.1). Additional subgroup analyses showed no difference between the two groups in patients with NIHSS ⩾ 20 (95%CI: -4.4 to 18.1) or NIHSS < 20 (95%CI, -10.8 to 8.8). Similar rates of symptomatic ICH (6.2% in the endovascular group and 5.9% in the IVT group; P = 0.83) and 90-d mortality (19.1% in the endovascular group and 21.6% in the IVT group; P = 0.52) were observed.

Enrollment and treatment of patients in the endovascular arm of this trial was not optimal. Over 20% of patients in the endovascular arm were included for analysis despite not receiving any endovascular therapy (due to lack of LVO on angiography). Notably, subgroup analysis of patients with LVO confirmed by CTA showed that endovascular therapy was associated with better functional outcomes than IVT alone (P = 0.01)[58]. The time to endovascular treatment was also significantly longer in the IMS Ⅲ trial compared to the previous IMS I and II trials. These earlier trials demonstrated that there is a close association between time to reperfusion and neurological outcome, with a linear decrease in probability of good neurological outcome with time[59]. Thus, this treatment delay may have reduced the clinical benefit of endovascular therapy in this trial. Lastly, of those treated, less than 5% were treated with stentrievers, either alone or in combination with other devices. This likely contributed to only 40% of patients achieving TICI grade 2b or 3 vessel recanalization[60].

SYNTHESIS Expansion

The SYNTHESIS Expansion trial[61] randomly assigned 362 patients with AIS within 4.5 h of symptom onset to either endovascular therapy (n = 181) or IVT (n = 181). Patients in the endovascular group who underwent treatment (n = 165) received either IA thrombolysis (n = 109) alone or in combination with mechanical thrombectomy (n = 56) without any prior IVT. Survival-free disability (mRS ⩽ 1) at 90 d, adjusted for key variables (age, sex, initial NIHSS grade and history of atrial fibrillation) did not significantly differ between the endovascular and IVT groups (30.4% and 34.8%, respectively; P = 0.16). Secondary outcomes including NIHSS score ⩽ 6, neurological deterioration, mortality, symptomatic ICH, and recurrent AIS also did not significantly differ between groups.

Again, the protocol of this trial likely resulted in enrollment of patients who were not suitable candidates for endovascular therapy under current recommendations. No preoperative imaging was required to confirm LVO prior to randomization, and a significant portion of patients (> 33%) had a NIHSS ⩽ 10. Additionally, the majority of patients in the endovascular arm received interventions that would no longer be considered standard of care. Only 13% of patients in the endovascular arm were treated with stentrievers[62], while 60% were treated with IA thrombolysis alone without mechanical retrieval. Because vessel recanalization rates were not reported, it is unclear if these patients received optimal therapeutic effect.

MR Rescue

The MR Rescue trial[63] randomized 118 patients with large vessel anterior circulation strokes to either mechanical thrombectomy (n = 64) or IVT (n = 54) within eight hours of symptom onset. Patient groups were also stratified based on pre-treatment imaging into favorable or non- penumbral patterns. Some studies have suggested that measuring the extent of salvageable brain tissue or ischemic penumbra on preoperative imaging may identify

patients who could preferentially benefit from endovascular therapy[64-67]. Favorable penumbral pattern was defined as a predicted infarct core of 90 mL or less and a proportion of infarct tissue within the at-risk region of 70 mL or less after pre-treatment magnetic resonance imaging or computed tomography. Results showed no significant difference in mean 90-d mRS observed among groups, both in the overall cohort (P = 0.99) or when stratified based on penumbral pattern (favorable, P = 0.23; non-penumbral, P = 0.32). No differences in the rates of symptomatic ICH (P = 0.24) or mortality (P = 0.75) were observed between groups. These results correlate with findings from a recent study which showed that a non-perfect preoperative ASPECT score did not significantly affect functional outcome[68].

No patients in the endovascular arm of the MR Rescue trial were treated with stentrievers. Similar to IMS Ⅲ, this likely contributed to the low overall rate of recanalization. Only 27% of patients in the endovascular arm achieved recanalization of TICI grade 2b or 3[60]. Additionally, this trial may have been underpowered due to the relatively low number of patients in each group.

Conclusions from Randomized Trials

While these trials provided valuable preliminary data for the assessment of endovascular intervention for AIS, each had significant limitations[60,62]. In SYNTHESIS and IMS Ⅲ, patients with LVO were not appropriately selected based on preoperative imaging. In all three trials, due to the pace of advancement in endovascular technologies, a minority of patients were treated with the most modern endovascular devices. Stentrievers were used infrequently in all three studies, which resulted in vessel recanalization rates below current standards. There is evidence that recanalization is associated with improved functional outcomes and reduced mortality[7]. Thus, the generalizability of the results from these trials to modern endovascular stroke practice is limited, and future randomized controlled trials are still needed.

As supported by the subgroup analysis of patients with CTA-positive LVO from the IMS Ⅲ trial, evidence still supports the use of endovascular mechanical thrombectomy for LVO within eight hours of symptom onset. Importantly, none of these trials raised questions about the safety of endovascular therapy. Recanalization is now possible in over 80% of cases, and for many patients, endovascular therapy is the only available treatment option. As endovascular devices and operator experience continue to evolve, improvements in patient outcomes are expected. Future trials will need to focus on proper patient selection and achieving optimal therapeutic effect (vessel recanalization) with modern endovascular devices[69]. Three ongoing clinical trials (THERAPY, SWIFT-PRIME, and POSITIVE) appear to have incorporated these key principles into their study design.

CONCLUSION

Endovascular mechanical thrombectomy involves the physical extraction of an occluding thromboembolus *via* grasping devices and/or direct/indirect aspiration. Over the past decade, advancements in catheter-based and endovascular device technology have led to strong improvements in rates of vessel recanalization. Initial randomized trials failed to show benefit of endovascular therapy over IVT, but limitations in study design have abated widespread acceptance of their conclusions. Future randomized trials evaluating endovascular mechanical thrombectomy for AIS will need to enroll and treat patients based off of the currently accepted standards of care.

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REVIEW

Epilepsy associated tumors: Review article

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Abstract

Long-term epilepsy associated tumors (LEAT) represent a well known cause of focal epilepsies. Glioneuronal tumors are the most frequent histological type consisting of a mixture of glial and neuronal elements and most commonly arising in the temporal lobe. Cortical dysplasia or other neuronal migration abnormalities often coexist. Epilepsy associated with LEAT is generally poorly controlled by antiepileptic drugs while, on the other hand, it is high responsive to surgical treatment. However the best management strategy of tumor-related focal epilepsies remains controversial representing a contemporary issues in epilepsy surgery. Temporo-mesial LEAT have a widespread epileptic network with complex epileptogenic mechanisms. By using an epilepsy surgery oriented strategy LEAT may have an excellent seizure outcome therefore surgical treatment should be offered early, irrespective of pharmacoresistance, avoiding both the consequences of uncontrolled seizures as well as the side effects of prolonged pharmacological therapy and the rare risk of malignant transformation.

Key words: Epilepsy; Low grade tumors; Long-term epilepsy associated tumors; Glioneuronal tumors; Ganglioglioma; Dysembryoplastic neuroepithelial tumor; Lesionectomy; Epilepsy surgery

Core tip: Long-term epilepsy associated tumors (LEAT) represent a frequent cause of focal epilepsies, particularly in children and young adults. Epilepsy associated with LEAT is generally poorly controlled by antiepileptic drugs while it is extremely responsive to surgical treatment. Temporo-mesial LEAT have a widespread epileptic network and complex epileptogenic mechanisms. The best management strategy of tumor-related focal epilepsies remains controversial representing a contemporary issues in epilepsy surgery.

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INTRODUCTION

Brain tumors, mostly low grade tumors, are associated with epilepsy in more than a half of cases and approximately 30% of tumor-associated epilepsy are pharmacoresistant.

Recent advances in neuroimaging and neurophysiology have allowed the recognition of subtle epilepsy-associated focal structural lesions, and have improved our understanding of the complex functional relevance of these lesions for seizure generation. Among this group of lesions the concept of long-term epilepsy associated tumors (LEAT) describes the wide group of low grade tumors in patients associated with chronic focal epilepsy[1-5]. Indeed, developmental brain lesions, in particular glioneuronal tumors (GNT), often associated with malformations of cortical development, in particular focal cortical dysplasia (FCD)[1,3,4], are among the most common causes of pharmacologically intractable epilepsy. In the setting of epilepsy surgery a brain tumor is the second most common cause of focal epilepsy[6] and it could be encountered in approximately 30% of patients operated on for refractory focal epilepsy[5,7,8].

Epilepsy associated-tumor is a debilitating condition, causing distress and adversely affecting the quality of life[3,5,9-17].

Epileptic seizure incidence varies according to tumour location and hystotype. Furthermore low-grade tumors often are more epileptogenic than high-grade tumours[8,10,12,13,16,18].

Epilepsy associated with brain tumours can be divided into two groups: tumors without other symptoms (usually low-grade tumors affecting children or young patients) or tumors together with neurological deficits (more frequently high-grade tumours in middle-aged and older patients)[10].

In the group of epilepsy associated with low grade tumors it is useful to further distinguish between the preeminence of oncological and epileptic logical aspects. In the group of the "diffuse low grade glioma" (LGG) the oncological aspects should prevail according to the progressive course of the neoplastic brain disease[10-12,15,16,19-22]. On the contrary in the group of LEAT, mainly represented by glioneuronal tumors (GNTs), epilepsy control should be the main goal[1,3-5,8,23-28].

The group of LEAT, is currently enlarging not only for the recognition of new, often rare, histotypes but also for the identification of tumors having hybrid and/or mixed features[3,29-32]. The biologic behaviour of LEAT is generally benign even if some tumors could present recurrence or malignant transformation[5,33]. New tumoral entities have been recently introduced and there is ongoing debate on improving consensus for diagnosis of LEAT between specialized centers[3,30]. While LEAT rarely coexist with hippocampal sclerosis (2%-25% of cases) they may often be associated with FCD (40%-80% of cases)[2,23,24,29,34-36].

LONG TERM EPILEPSY ASSOCIATED TUMORS

The histological characteristics of these tumors influence their propensity to generate seizures.

Gangliogliomas

Gangliogliomas (GG) are the most common neoplasm causing chronic focal epileptic disorders (about 40%)[5,37-39]. GG can occur in any part of the central nervous system, although the temporal lobe is the most common location[5,33,40] followed by the frontal lobe, the optic pathway, the spinal cord, the brainstem, the cerebellum and the pineal gland.

Dysembryoplastic neuroepithelial tumors

Dysembryoplastic neuroepithelial tumors (DNT) are grade I WHO tumors with cystic components, described by Daumas-Duport *et al*[41] in 1988 as a typically cortical tumor affecting children and young adults with long-standing, drug-resistant epilepsy. Most frequently DNT are sited in the cortex of temporal lobe above all at the temporo-mesial site[42-46]. Rarely DNTs have been described in ectopic locations (septum pellucidum and the caudate nucleus)[47] in the pons, thalamus, basal ganglia, cerebellum, third ventricle, and brainstem. Familial occurrence of these neoplasms have been described.

Pleomorphic Xanthoastrocytoma

Recently also pleomorphic Xanthoastrocytoma (PXA) has been considered part of this group of tumors. In fact, in addition to the astrocytic nature, there is growing evidence that PXA exhibits some histological, immunophenotypic and ultrastructural neuronal features[48,49]. Furthermore occasionally, FCD can be associated with PXA.

Papillary glioneuronal tumor

Firstly described by Kim *et al*[50] 1997, Papillary glioneuronal tumor (PGNT) most frequently arises in a supratentorial locationwith rare case showing multilobar involvement[3]. At MRI they appear as a cystic enhancing lesion with solid areas and often a mural nodule. PGNTs affect young adults.

Pilocytic astrocytoma

Supratentorial pilocytic astrocytoma (PA) is frequently presents with chronic epilepsy. PA are included within the common histological entities encountered in series of tumor-associated epilepsy cases[3,5,30,51].

Diffuse astrocytoma

Diffuse astrocytomas mostly arise in the cerebral hemi-

spheres of young adults (frontal and temporal cerebral lobes) and seizures represent one of the most common symptoms. It has been described in the group of LEAT[52]. Some author stated that initial presentation with seizures could influence long-term survival[30,53].

Oligodendroglioma

Oligodendrogliomas usually arise in the cerebral hemispheres of young adults. They belong to LEAT group. Seizures represent a common presenting symptom[5,5,30].

Angiocentric gliomas

low grade cerebral tumor mostly affecting children and young adults and it is more and more frequently identified in the setting of chronic epilepsy[3]. Angiocentric gliomas (AG) have a cerebro-cortical location, often with involvement of the fronto-parietal and temporal lobe.

Extraventricular neurocytoma

This rare entity, may be considered in the spectrum of GNT associated with focal epilepsy[29].

LEAT with mixed tumor features

"Hybrid" tumors constituted by mixed forms of gangliglioma and DNT but also PXA and gangliglioma, PXA with DNT and, PXA with an oligodendroglioma have long been recognised, representing an increasing group of tumors in epilepsy surgical series. Cases where a PA developed within a DNT, as well as PA grew in combination with a low-grade oligodendroglioma, have been noted[54,55].

TUMOR SITE

In the setting of low grade tumors associated with epilepsy, diffuse LGG (WHO grade Ⅱ gliomas) are mainly found in the insular, fronto-insular, temporo-insular regions (namely paralimbic structures) representing the iso-mesocortical transition zone[56].

Instead, LEAT mainly arise in the temporo-mesial structures (namely limbic lobe) in the site of allo-isocortical transition, harboring more frequently a neuronal differentiation maybe due to their proximity to the hippocampal granular layer where neurogenesis during adult life takes place[56-62].

In our findings[8,26,28,36] according with others[62-65] in the mesial temporal lobe both the lesion and hippocampus seem to be epileptogenic even if there are no other MRI abnormality (hippocampal sclerosis) and pathological examination shows normal findings.

PATHOGENESIS OF TUMOR-ASSOCIATED SEIZURES

Epileptogenesis of brain tumors depends on the histotype and location, even if the complexity of structural and molecular changes implies a multifactoriality of the pathogenesis[10,28,66,67] and may differ according to histologies (GNT *vs* diffuse low grade gliomas)[4,10,15,16,68,69]. The comprehension of the epileptogenesis in GNT is crucial to treat effectively pharmacologically intractable epilepsy (as discussed above) represents the initial, and often the only, clinical manifestation of the tumor and critically affects the patient's daily life.

LEAT are often large tumors, with a high propensity to develop seizures when located in temporal or frontal lobes[10,70]. GNT are composed of peculiar cellular components with hyperexcitable neurons, functionally integrated into excitatory circuitries, and neurochemical characteristics that can be relevant for epileptogenesis[34]. Data provided by intralesional EEG recording have demonstrated intrinsic epileptogenicity of GG and DNT[71,72]. In addition, immunocytochemical studies showing high expression of specific glutamate receptors (GluR) subtypes suggest a hyperexcitability in the neuronal constituent of GNT[73,74]. An additional mechanism that can sustain epileptogenesis is related to an unbalance between excitation and inhibition due to to a prominent expression of mGluR5 and downregulation of several gammaaminobutyric acid (GABA-A) a receptor (GABA-AR) subunits that suggest an impairment of GABAergic inhibition[75,76]. Furthermore, a disturbed ion homeostasis and transport could represent an additional potential mechanism leading to increased excitability in GNT[9,77].

Another potential epileptogenic mechanism is related to a possible role of inflammation in the pathophysiology of human epilepsy[78]. Proinflammatory molecules have been shown in experimental models to decrease the seizure threshold[78,79] and may be involved in the generation of seizures in brain tumors, particularly in GNT[80]. Different mechanisms can cause an increment of neuronal excitability, for instance by enhancing the extracellular glutamate concentrations, as well as modifying the function of both glutamate and GABA receptors. Furthermore in GNT, particularly in GG, inflammatory changes have been showed to be associated with evidence of alterations in blood-brain barrier (BBB), with albumin extravasation and uptake in tumor astrocytes[66,81]. Interestingly, some data have shown also a prominent upregulation of the mTOR pathway, known to be a key regulator of cellular changes involved in epileptogenesis in GNT, particularly in GG[82,83].

Several other additional mechanisms have been hypothesized to account for enhanced excitability in GG, such as for example, hypoxia and acidosis, ionic changes, and deposition of hemosiderin in the peritumoral region[10]. Enzymatic changes may also occur in peritumoral tissue, impairing neurotransmitter synthesis and storage, and contributing to tumor-associated epilepsy. Finally, association with cortical dysplasia (as discussed below) also has to be considered in the evaluation of the epileptogenicity of GG. Indeed the identification of a coexistent pathology may be clinically relevant since it has been extensively reported that the tumor itself may be electrically silent and the origin of seizures is from a pathological tissue adjacent to the tumor[42,77,84]. The implication is that excising the tumor and leaving in place the nearby abnor-

mal epileptogenic tissue, may give unsatisfactory results on the seizure outcome. Young age and long duration of illness are associated with an increased risk of secondary epileptogenesis. GNT can be intrinsically epileptogenic, even when associated with FCD[71].

CLINICAL AND EEG FEATURES OF FOCAL EPILEPSY ASSOCIATED WITH LEATs

Clinical features

Focal epilepsy is the most common and often the only symptom of LEAT. Neurological deficits are relatively uncommon, varying from 0% to 15% according to different series: the neurological sparing might depend on the indolent and slow course of LEAT that might allow compensation of possible brain impairment by slowly developing plastic processes, particularly in the young age. Epilepsy can appear at any age: however, the majority of cases present with an epilepsy onset in adolescence and young adulthood. In DNET, seizures appear almost always and more than half of the patients have focal seizures with alterated consciousness, with or without secondary generalization[85]. Regarding GGs, 80%-90% of patients seizures represent the only clinical symptom (mainly secondarily generalized tonic-clonic seizures)[86,87]. As already reported, the most common location of GG is the temporal lobe where they are frequently positive to CD34 glycoprotein staining. On the contrary it is not reported the association with CD34 for GG located in other sites of the brain[37,86-88]. It could be argued that this protein might represent a marker of dysplastic differentiation and that it could contribute to epileptogenesis. Seizure semiology is related to the site of tumor. In general, complex partial seizures with aura are more common in LEAT located in the temporal lobe, whereas secondary generalization is more common in epilepsies associated with extratemporal LEAT[39]. However, the extension of the tumor-related epileptogenic area may vary according to the anatomical location of the neoplasm: in fact, several data suggest that epileptogenic zone may be more widespread and complex in focal epilepsies associated to LEAT in the mesial temporal lobe in comparison to neocortical temporal lateral locations[36,40,61,65]. Occurrence of status epilepticus has been reported to be rare. Clinical parameters that differentiated patients operated on in childhood from patients operated on in adulthood were: (1) aura that was reported more often in the adult group, but it should be noted that this finding might at least partially depend on the fact that, in general, children are less able to refer their auras; and (2) mean age at seizure: probably due to the fact that developing brain has a low seizure threshold which leads to early and frequent seizures. Moreover, in pediatric age, malformations of cortical development are most often the basis of lesional epilepsy that is characterized by a high seizure frequency that can facilitate an early diagnosis and that can lead to early evaluation for a surgical approach. No differences between the clinical features of epilepsy associated with DNET and with GG have been reported[42,89]. A favorable seizure outcome has been observed in cases with a short duration of epilepsy, only partial seizure and the lack of secondary generalization . Response of GNT-associated epilepsy to antiepileptic treatment is variable, but drug-resistance is quite common[5,39,42,90].

Task Force of the ILAE Commission on Therapeutic Strategies defined drug resistant epilepsy as the failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug (AEDs) schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom[91].

Several explanations could be at the basis for drug resistance. AEDs could be affected by the biochemical milieu of the peri-tumoral space.

Furthermore significant interactions between AEDs and other drugs (*i.e.*, chemoterapeutics) may decrease antiepileptic effectiveness, while increasing side effects interfering with the hepatic cytochrome P450 system. Furthermore AEDs resistance might result from over expression of multi-drug resistance-related proteins (MRPs) in tumors (particularly in capillary endothelial cells and astrocytes), which restrict the penetration of lipophilic substances into the pathologic tissue[10].

EEG features

Usually interictal EEG shows spikes and/or, sharp waves, sometimes intermixed with slow activities; in some instances normal EEG have been reported. These abnormalities, in preoperative EEG are commonly lateralized to the tumor side, less often to the correct lobe. However, Morris *et al*[39] (1998) reported that the occurrence of interictal EEG abnormalities and ictal EEG onset in correspondence of the site of the tumor may not be predictive of seizure outcome; indeed, in some cases a post-operative poor seizure outcome has been reported in patients with EEG interictal and ictal findings perfectly concordant with tumor location. On the other hand, also patients with EEG slow or epileptiform abnormalities distant from the tumor site or with ictal EEG onset non-localized or widespread to a whole hemisphere improved regarding seizure outcome after tumor resection[39]. In temporal lobe GNT, long-term video-EEG monitoring may allow recording of seizures and identification of the epileptogenic zone; indeed, several data suggest that in mesial temporal lobe GNT a tailored resection that include, besides the tumor, the epileptogenic area as defined by the anatomic and electroclinical correlations performed on the ictal video-EEG data, provides better post-operative seizure outcome as compared to simple lesionectomy[36,45,61,92,93]. In cases of undetermined lateralization of seizure focus, invasive EEG investigations may provide useful information, although in GNT-associated focal epilepsy the main goal of intracerebral recordings is usually to map eloquent cortex in proximity of the neoplasm. Several reports focused on prediction

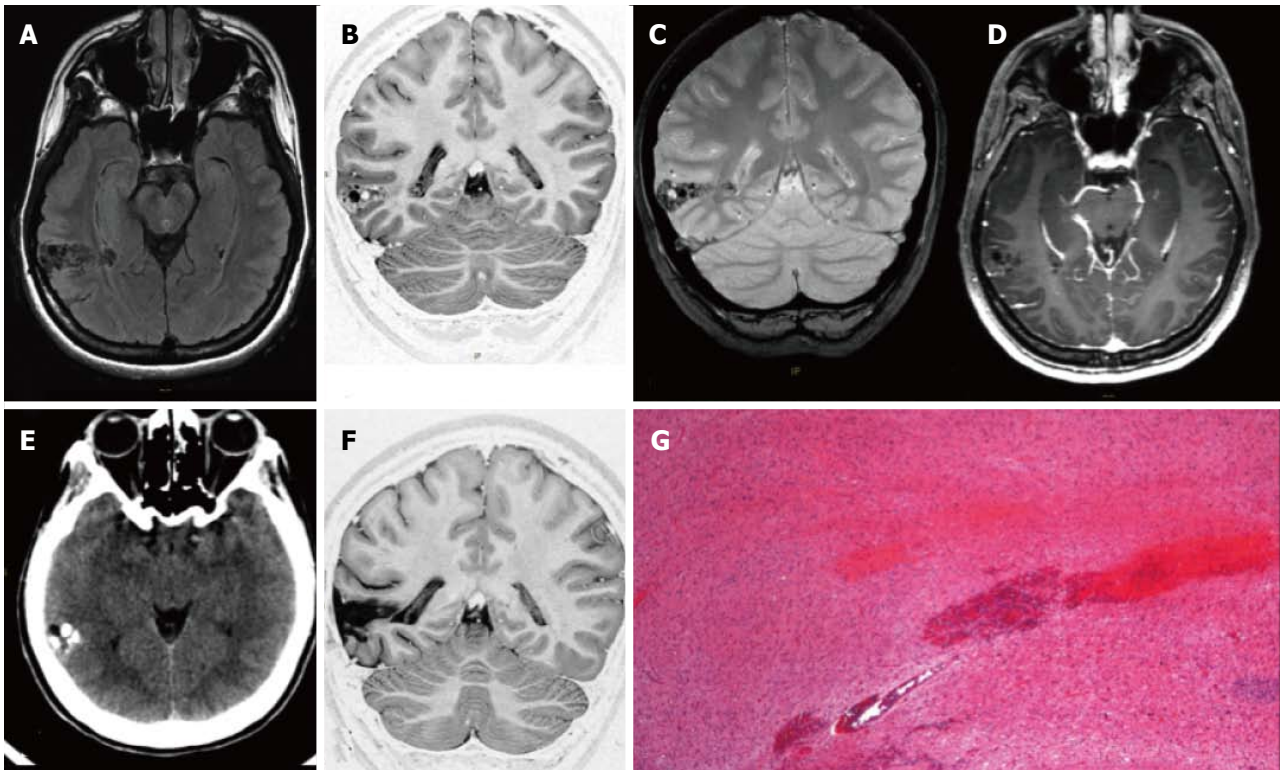

Figure 1 Ganglioglioma World Health Organization grade I of the right posterior middle temporal gyrus. Axial FLAIR T2-w (A) and coronal IR T1-w (B) images show inhomogeneous cortical-subcortical mass extending within the deep white matter and reaching the ependymal layer. The tumor presents a combination of solid, cystic and calcified components. The latter is better identified on coronal T2*-w sequence (C). Post-contrast axial T1-w image (D) shows no pathological enhancement and axial CT scan (E) confirms the calcified component. Coronal IR T1-w image (F) demonstrates lesion resec-tion; G: Histological examination evidences a biphasic neoplastic population, with neu-ronal and glial elements.

of poor postoperative outcome by identifying ECoG spike discharge patterns in FCD and the persistence of seizure patterns or continuous epileptiform discharges in post-resection ECoG recordings . There are little evidences about the ECoG discharge patterns in patients with GNTs because of the small numbers of patients investigated[89,93,94]. Different disorders (LEAT and FCD) may have similar electrocorticographic abnormalities probably due to the common developmental origin. In these cases have been observed continuous spiking (more often in FCD), bursts, and recruiting discharges. When continuous spiking is found in GNT, it is likely to be due to associated dysplastic regions with a high neuronal density[45,93]. A recent study employed MEG to investigate possible differences in whole brain topology of epileptic glioma patients, comparing them to patients with non-glial lesions and healthy controls. LGG patients showed decreased network synchronizability compared to healthy controls in the theta frequency range (4-8 Hz), similar to patients with non glial lesions. Network characteristics are associated with clinical presentation (seizure frequency in LGG), and with poorer cognitive performance (both low grade and high grade glioma) suggesting that histology could partly determine differences in epileptogenesis and epileptic probably due to differences in cortical plasticity. Interestingly, it would seem that low grade glioma and non tumoral lesions have a decreased synchronizability that could predispose to a high occurrence of seizures and cognitive decline.

IMAGING

Gangliogliomas and gangliocytoma

The differentation between GG and gangliocytoma (GC) is mainly based on histology. They may have variable tumour size (2-3 cm) and a typical location at the periphery of cerebral hemispheres. There is usually little associated mass effect and peripheral vasogenic edema and superficial lesions may expand cortex and remodel bone.

The MR signal of GG is variable and inhomogeneous due to the presence of a combination of solid, cystic and calcified components[46,95] (Figures 1-4).

Calcifcations can be more conspicuous as areas of hypointensity on T2* gradient echo weighted images, or even more evident at unenhanced CT (Figure 1E).

Medium contrast enhancement could be variable: nodular, intense and homogenous (Figure 3E); "ringlike" appearance (Figure 4C) but also nonenhancing (Figure 1D). Although extremely rare GG may show focal leptomeningeal involvement (Figure 4C).

Dysembryoplastic neuroepithelial tumor

DNET are well-demarcated, wedge shaped, multinodular, "bubbly" intracortical tumors often similar to other LGG.

DNET may show a multicystic morphology more

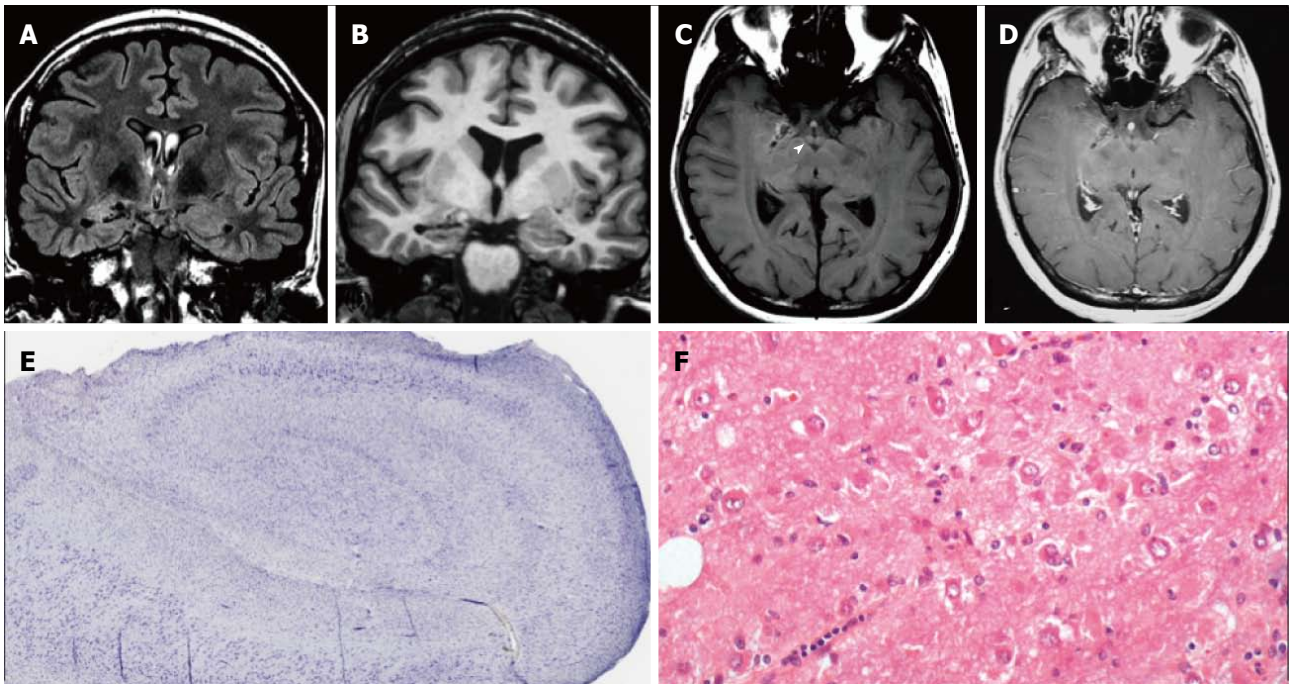

Figure 2 Gangliocytoma and Mesial Temporal Sclerosis MTS (dual pathology). Coronal Flair T2 (A) and T1-w images (B) demonstrate a right hippocampal atrophy with signal hyperintensity on FLAIR. The ipsilateral temporal horn is dilated. Axial T1-w pre- (C) and post-contrast injection (D) show a non-enhancing multicystic lesion with calcification near the optic tract. The right mammillary body is atrophic (arrowhead); E: Neoplastic ganglion cells exhibit disorganized clusters and show abnormal cytologic features; F: Hippocampal specimen displays ILAE hippocampal sclerosis type 1, with severe pyramidal cell loss in both CA1, CA3 and CA4 sectors.

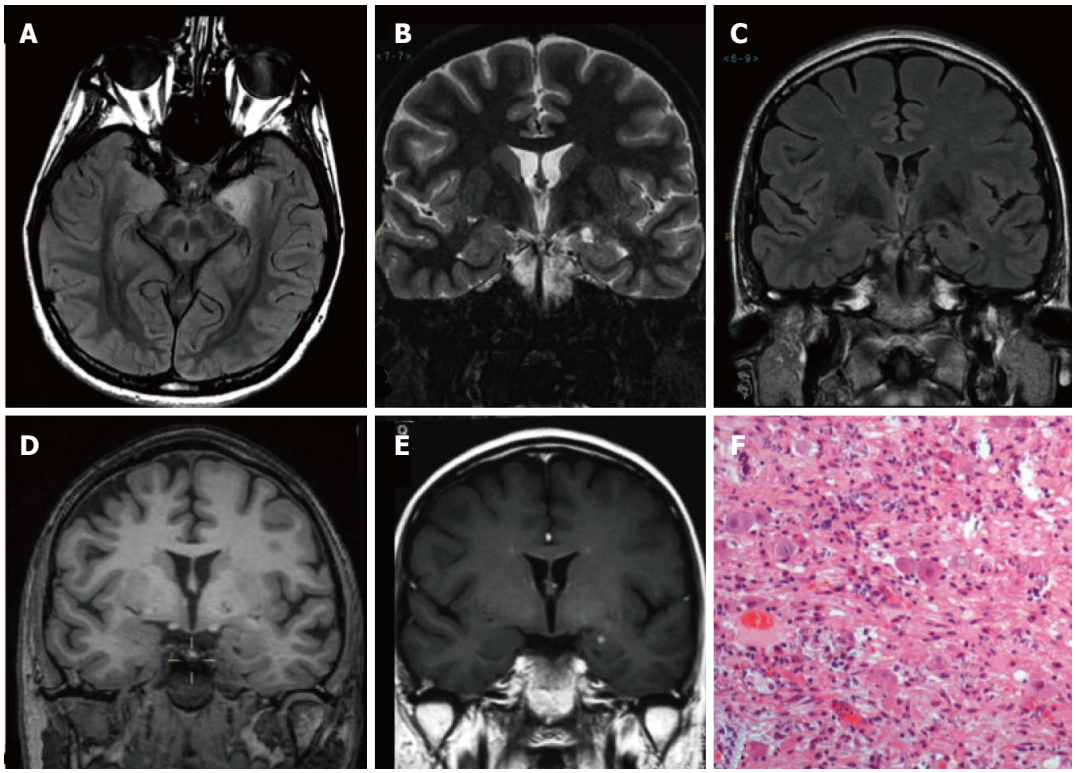

Figure 3 Ganglioglioma World Health Organization grade I of the left temporo-mesial cortex. The tumor shows heterogeneous cortical-subcortical high signal on axial proton density weighted image (A). It appears partially cystic on coronal IR T1 (B) FLAIR T2 (C), T1 (D) weighted sequences. Post-contast T1-w image displays nodular, intense and homogenous enhancement (E). Low-magnification view shows a vaguely lobulated, hypocellular vascularized neoplasia, with scattered lymphocytic infiltrates (F).

frequently than GG. Absent or very slow increase in size over time is typical of DNET, and recurrence is also extremely rare. Contrast enhancement could be found in about 30% of cases.

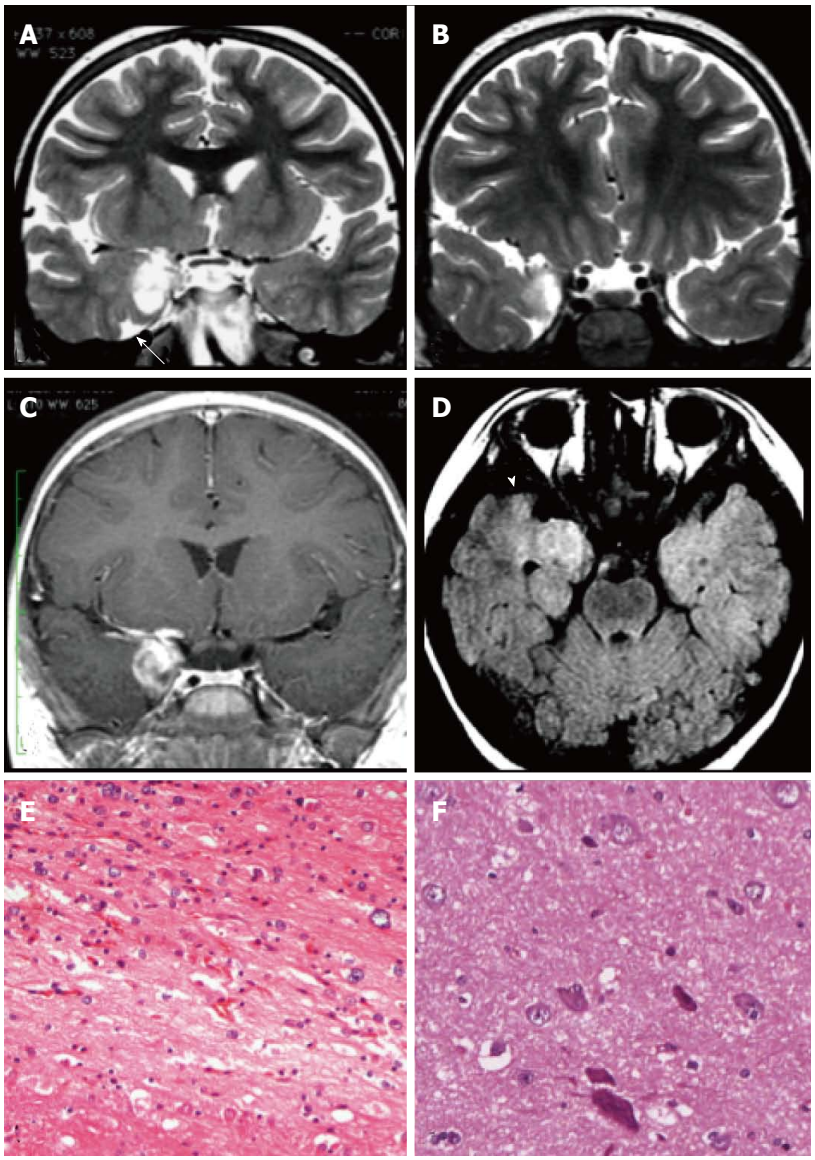

Figure 4 Ganglioglioma and associated focal cortical dysplasia IIa. Coronal FSE T2-w (A, B) demonstrate a temporo-mesial heterogeneously hyperintense lesion. Post-contrast coronal T1-w (C) shows enhancement of the tumor and adjacent leptomeninges. A signal abnormality extending from the surface of the ventricle to the pole (arrowheads in D) and adjacent anomalous sulci (arrow in A) were suspicious for FCD, subsequently histologically confirmed. Microscopy evidenced a tumor composed of ganglion cells intimately intermixed with astrocytic elements (E) and focal cortical dysplasia with dysmorphic neurons (FCD Type IIa) (F).

On CT scan the tumor appears as a cortical-subcortical hypoattenuating mass with sporadic calcifications. Scalloping of the adjacent inner table of the skull may also be present. At MR imaging, DNET most commonly manifest as pseudocystic, multinodular cortical masses that are hypointense on T1-weighted images and hyperintense on T2-weighted images with minimal or without mass effect and surrounding vasogenic edema (Figures 5 and 6).

Some lesions may expand involving cortical gyri and, producing a soap bubble appearance at the cortical margin. (Figures 5 and 6).

Pleomorphic Xanthoastrocytoma

PXA classically, although not specifically, appear as cystic supratentorial mass containing a mural nodule and involvong cortex and adjacent leptomeninges[96]. PXA is usually a circumscribed and slow growing lesion, that rarely recurs; size and morphology are variable.

At unenhanced CT the tumor appears as a hypo or isoattenuating mass. Calcifications are rare. On MRI T1-WI PXA are usually hypo to isointense displaying inhomogenous, mainly iso-hyperintense, signal intensity on T2-weighted sequences. Peritumoral edema is relatively uncommon. They usually enhance after gadolinium injection (Figure 7). Leptomeninges contrast enhcement is highly characteristic[97].

Extraventricular neurocytoma

Extraventricular neurocytoma may be difficult to differentiate from other types of low-grade tumor, such as GGs or DNET. It could be a well circumscribed, heterogeneous and variably enhancing mass. CT and MRI aspects depend on the cellularity and degree of calcification. They may have peritumoral oedema and intralesional cyst but rarely intralesional bleeding[29,98,99].

Pilocytic astrocytoma

Pilocytic astrocytomas are the most common form of glioma in childhood and most frequently manifest in the first two decades of life[100]. They may arise anywhere within the neuraxis, but among the pediatric population

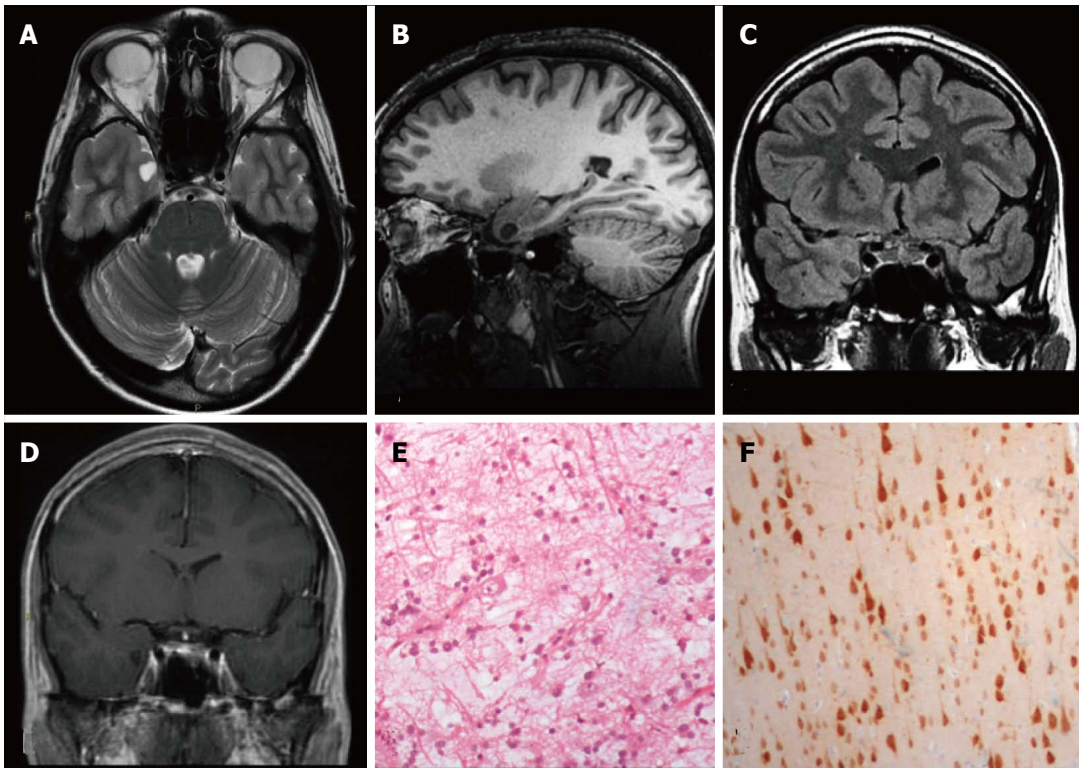

Figure 5 DNET of the right uncus. Axial T2-w (A) and sagittal 3D T1-w (B) reveal a cystic cortical mass well-demarcated, without perilesional oedema or mass effect. On coronal FLAIR T2-w image (C) the tumor is variably hypo- and isointense. Post-contrast axial T1-w sequence (D) shows no enhancement. Histological examination shows a tu-mor characterized by the "specific glioneuronal element", typical of DNET, (E), while the cortex adjacent to the tumor displays cortical lamination abnormalities compatible with FCD type IIIb (F); the latter was not depicted at MR study.

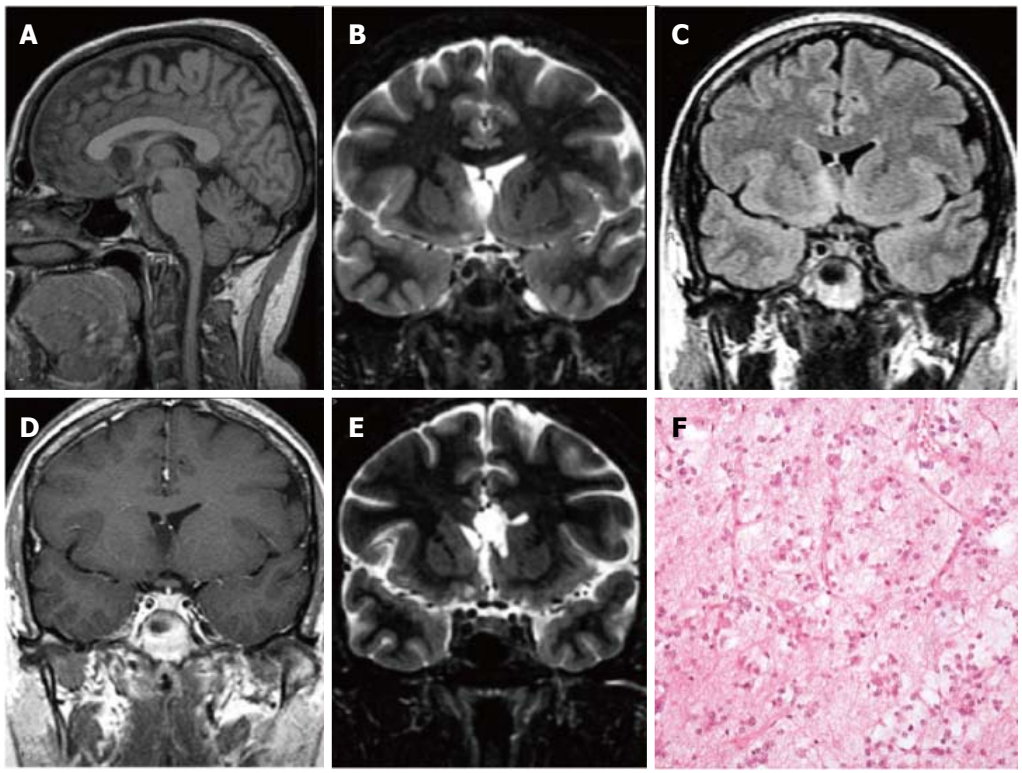

Figure 6 Extra temporal DNET. Sagittal 3D T1 (A) coronal IR T1 (B) and FLAIR T2-w (C) demonstrate a cystic wedge-shaped lesion in the right fronto-orbital gyrus. On FLAIR T2-w the tumor is slightly hypointense with a faint hyperintense rim. On post contrast coronal T1-w images there is no enhancement uptake (D); E: Post-surgical scan on cor-onal IR T1-w; F: Microscopic study evidences the presence of floating neurons, a feature of DNET, in microcystic areas lined with oligo-like cells.

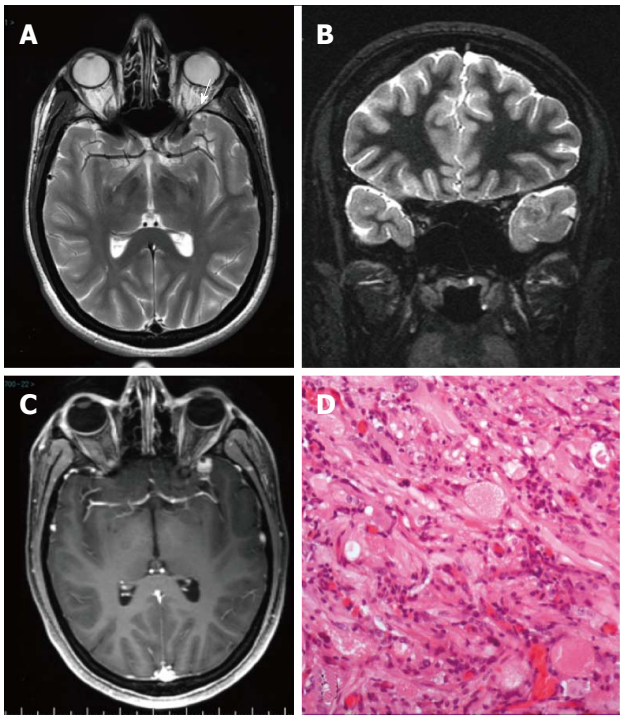

Figure 7 Pleomorphic xanthoastrocytoma World Health Organization grade II. Axial T2 w (A) and coronal IR T1-w (B) images show temporo-polar mixed signal intensity cortical mass with a small cystic component anteriorly (arrow in A). Post-contrast coronal SE T1w (C) shows a well-delineated, peripherally located enhancing nodule. (D) Microscopically the tumor is characterized by huge cytologic atypia, a vaguely fascicular arrangement and scattered eosinophilic granular bodies.

they are more frequently found infratentorially. Optic nerves, optic chiasm and hypothalamus, basal ganglia, and thalamus represent other common localtions. Cerebral hemispheres involvement has been less frequently described[100].

Pilocytic Astrocytomas are commonly characterized by fluid accumulation, with subsequent cyst formation and by mural nodule or a rim of tissue surrounding the cyst that enhances on post-contrast imaging. Predominantly solid mass lesions with minimal or no cyst have been described[101] (Figure 8).

Calcification may be seen in up to 25% of cases and haemorrhage has been reported. On MRI the solid portion of the neoplasm is typically isointense to hypointense on T1 weighted images and hyperintense on T2 weighted sequences to grey matter and it enhances after gadolinium chelates injection (Figure 8D). The signal intensity of the cystic portion is often not suppressed on FLAIR T2 weighted images due to its protein content.

MR spectroscopy reveals elevation in choline and reduction in NAA, with minimal elevation in lipid peak (Figure 8F). Lactate peak could be elevated, representing alteration in mitochondrial metabolism or variability in glucose uptake[102].

Diffuse astrocytoma

Diffuse astrocytomas are diffusely infiltrating primary brain neoplasms of astrocytic origin that are classified as WHO grade Ⅱ.

Diffuse astrocytomas are usually at unenhanced CT iso to hypoattenuating lesions. They do not enhance on post-contrast imaging. Calcifications may be present in approximately 20%; cyst formation is rare.

MRI demonstrates astrocytomas as relatively homogenous mass involving and expanding more typically cerebral hemispheres cortex and adjacent white matter. The lesions are high in water content, thus appearing as hyperintense on T2 weighted images and hypo isointense on T1 weighted sequences. They usually lack peritumoral oedema (Figure 9).

Well differentiated Astrocytomas has a variable appearance after contrast agent administration, but usually shows no significant contrast enhancement (Figure 9C). In general, contrast enhancement is not recognized as a reliable indicator of the grade of infiltrative astrocytomas. MR perfusion imaging however seems to be more informative for distinguish low- and high-grade astrocytoma and for identifying low-grade lesions that could more likely behave aggressively[103].

On dynamic contrast enhanced T2* weighted MR perfusion imaging study rCBV is typically less than 1.75 (Figure 9D)[104].

MR Spectroscopy should display Cho elevation and NAA reduction. A High myo-inositol to Creatine ratio (Myo/Cre) in also present (Figure 9E)[105].

FOCAL CORTICAL DYSPLASIA AND LEAT

LEAT and focal cortical dysplasia FCD are common findings in drug-resistant focal epilepsies, and frequently coexist[1,6,8,24,34,36,104,106-109].

Rarely MRI features of LEAT could be misinterpreted as FCD. Generally most important neuroradiological findings in FCD are increased cortical thickness, blurring of the cortical-white matter junction, increased signal on T2-W, a radially oriented linear or conical transmantle stripe of T2 hyperintensity, cortical thinning, and localized brain atrophy[34,110-112] (Figure 10).

Some limitations are encountered in the correct identification of different FCD types or subtypes[111-114]. A high number of false negatives is detected with FCD type I and slightly fewer with FCD type Ⅱa (about 50% sensitivity). FCD Ⅱb is much more easily identified (about 90% sensitivity)[112,113] (Figure 10).

Association between LEAT and FCD poses further issues into its correct identification. In a limited serie of patients with LEAT, who underwent surgery at our Institution associated FCD has been correctly identified in the majority of cases[113] (Figure 4). In a few cases peritumoral edema and neoplastic infiltration both caused subcortical white matter signal alterations, determining false positives (FP) and false negatives (FN) FCD results. Indeed, the signal abnormality is able to mimic a blurring, but it could hide a FCD contiguous to the tumour (Figure 11).

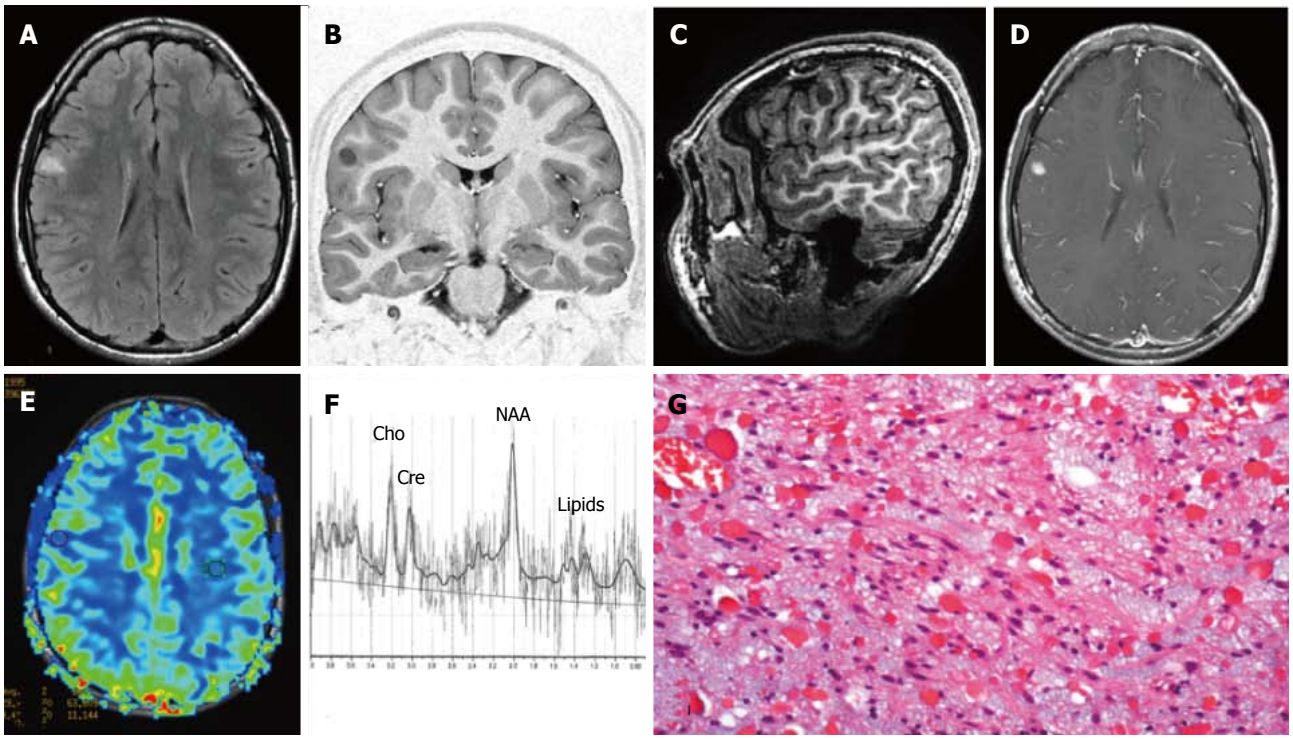

Figure 8 Pilocytic astrocytoma World Health Organization grade I of the right frontal lobe. Axial FLAIR T2-w (A) and coronal IR T1-w (B) images show a cortical-subcortical lesion, with cystic component, with minimal mass effect. The tumor appears well de-marcated (C) on 3D sagittal sequence and displays nodular and homogeneous en-hancement on post-contrast axial T1-w images (D). Perfusion study doesn't show any rCBV increase within the lesion (E). MR Spectroscopy (MRS) study (F) reveals elevation in choline and reduction in NAA. (G) Histological examination shows a tumor com-posed of areas rich in myxoid material, elongated glial elements with uniform nuclei and numerous eosinophilic granular bodies.

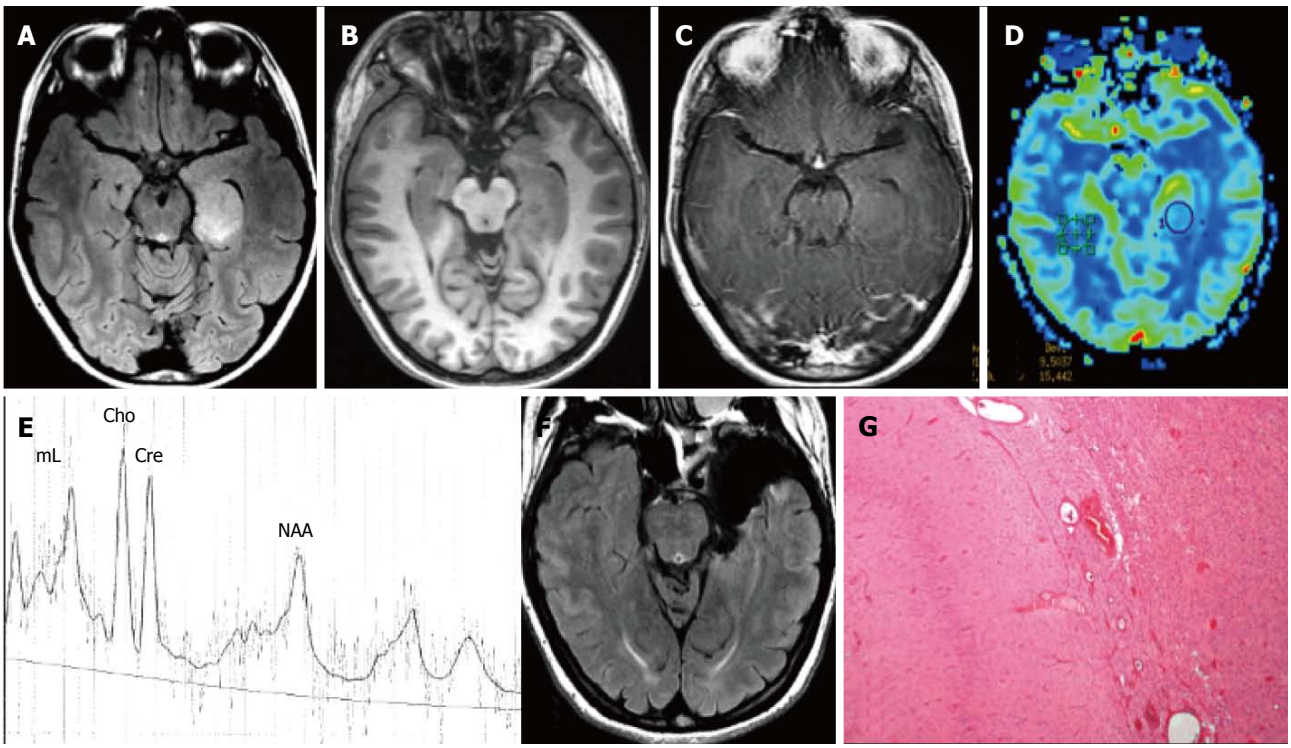

Figure 9 Temporo-mesial astrocytoma World Health Organization grade II. Axial FLAIR T2-w (A) shows a left temporal hyperintense mass, involving mainly the hippocampus. The lesion is slightly hypointense on T1-w image (B) and does not demonstrate enhancement after gadolinium injection (C). Perfusion study reveals no significant rCBV increase (D). MRS study shows a faint NAA reduction, a slight Cho elevation and high mI, expression of low grade glioma (E). Postsurgical axial FLAIR T2-w (F). (G) This histological picture exhibits in the left side a portion of hippocampus and in the right side an infiltrating astrocytoma, composed of fibrillary elements with varying degree of hypercellularity.

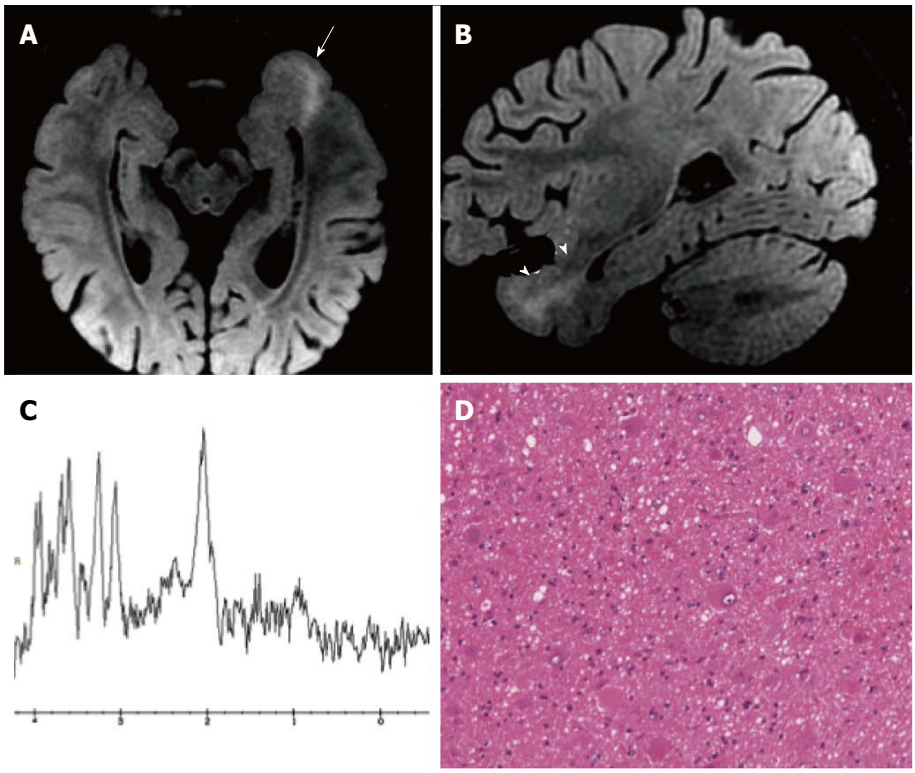

Figure 10 Focal cortical dysplasia with balloon cells (Taylor). Axial (A) and sagittal (B) reformatted fat-saturated 3D FLAIR images show a left temporo-mesial cortical thicken-ing (arrow) and white matter tapering to the temporal horn of the lateral ventricle (arrowheads). MR spectroscopy shows normal metabolite concentrations (C). (D) Histol-ogy demonstrates the presence of typical balloon cells, showing large and opalescent glassy eosinophilic cytoplasm.

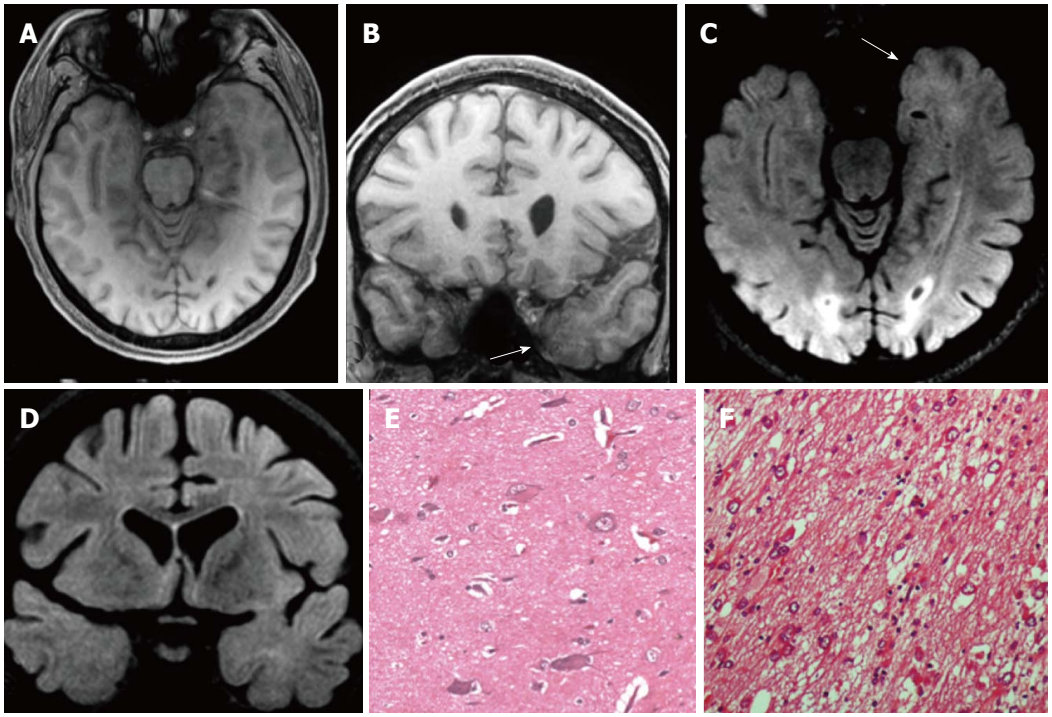

Figure 11 Gangliogliomas World Health Organization grade I of the left temporo-mesial region and focal cortical dysplasia IIa subtype associated. Axial and coronal T1-w images (A-B) show thickening of amygdala and uncus (arrow in B). Axial and coronal FLAIR T2-w images (C-D) present blurring and adjacent subcortical high signal abnormality compatible with a focal cortical dysplasia (FCD). Microscopy evidenced a glioneuronal tumor, with scattered binucleated ganglion cells, compatible with a gan-glioglioma (E) and dysmorphic neurons in the adjacent cortex (FCD Type IIa) (F).

These limitations were more evident when tumour size is larger (Figure 12). MRI sensibility can be reduced

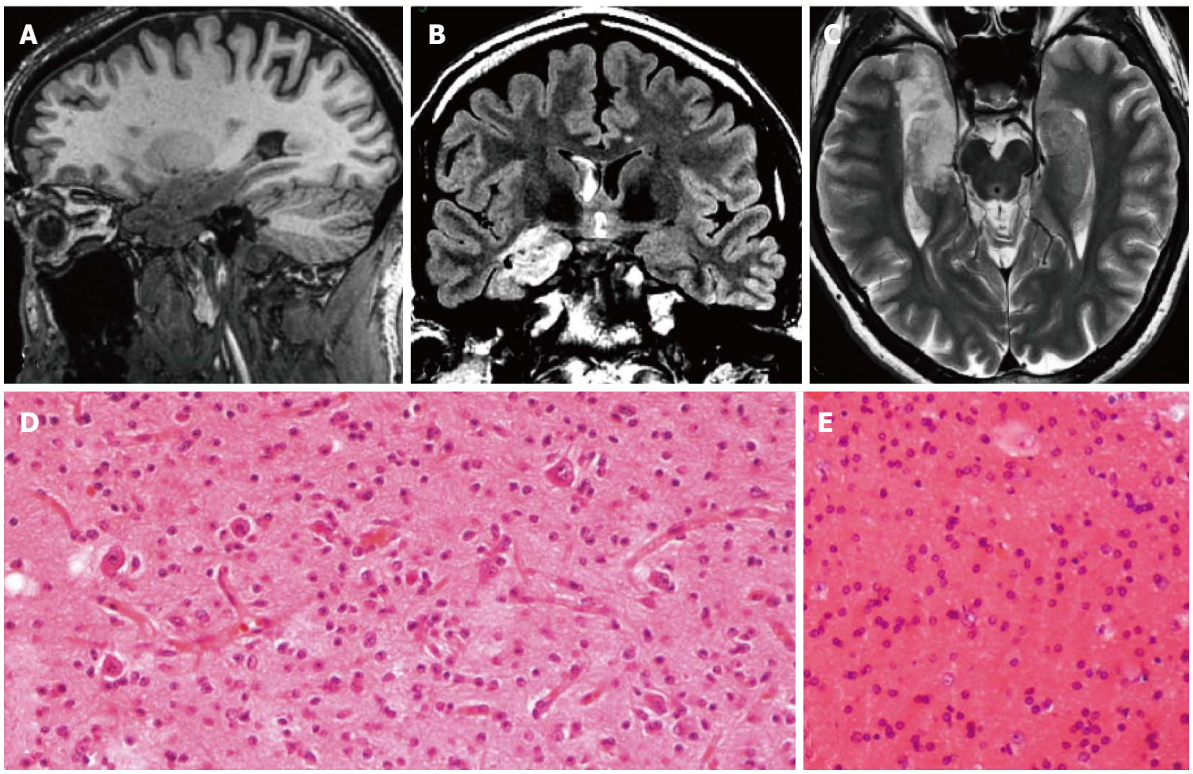

Figure 12 Gangliogliomas and focal cortical dysplasia IIa. Sagittal 3D T1-w (A), coronal FLAIR T2-w (B) and axial T2-w (C) reveal an inhomogeneous mass, involving the right hippocampus and the temporal pole. Due to the size of the tumor, the associated dysplasia is not clearly visible. Histological examination demonstrates the presence of a glioneuronal tumor with small ganglion cells in a desmoplastic stroma (D) and of dysmorphic neurons in the adjacent cortex (focal cortical dysplasia Type IIa) (E).

by an incomplete protocol too.

MOLECULAR ASPECT OF LEAT

The following molecular markers may facilitate differential diagnosis of LEAT: (1) IDH1 and IDH2 mutations: common in low grade diffuse gliomas (70%-80%), while they are generally not present in PA and GNT[115]; (2) LOH 1p/19q: constitutes the keystone in diagnosis of oligodendrogliomas (> 70% of tumors), while it has not been detected in DNT, a useful difference in those cases in which histological aspects do not permit a conclusive diagnosis[116]; and (3) BRAF V600E mutations: frequently found in PXA, GG and PA, whereas diffuse grade Ⅱ gliomas harbor only rarely these mutations[117].

As recently observed these BRAF-mutant grade Ⅱ diffuse gliomas seem to present with refractory seizures and frequently are located within the temporal lobe.It as been proposed that BRAF mutations could be strictly linked to epileptogenesis[118].

Interestingly we found that BRAF mutations could be present in the FCD associated with LEAT, suggesting a pathogenetic role of BRAF mutations in cyto-architectural dysplasia and in the tumorigenesis of LEAT[109].

SURGICAL STRATEGIES FOR LEAT

Epilepsies associated to LEAT are usually unsatisfactorily controlled by antiepileptic drugs, whereas excellent results can be achieved by surgery[4,5,26,28,42,65,92,119]. Various surgical approaches have been adopted for the radical resection of these tumors. The choice of surgical approach is also related to the goal of surgical strategy.

The surgical strategy may be directed only to oncological issues and/or to resolve epilepsy. In this last condition we must have an epilepsy surgery oriented approach.

A non-invasive presurgical study and neuropsycological assessment**,** may define the extension of the epileptogenic zone and may address the choice of the better surgical strategy to optimise seizure control (lesionectomy or tailored resection)[24,26,28,36,120].

Rarely in the setting of epilepsy associated tumor may be necessary an invasive presurgical study (using subdural grid, depth electrodes, or stereo-EEG)[24,64,121-123]. LEAT are certainly the prototype of cases where epilepsy is the main problem. However, in recent years, even in cases where the main problem is oncological, it is becoming equally important trying to preserve brain functions and to best cure even epilepsy (especially when tumors involve mesiotemporal structures, the insular lobe, or the central area) in order to improve the quality of life[15,63,64,124].

Several authors analyzed epileptological outcome according to surgical treatment in tumor-related chronic epilepsy. While some argue that lesionectomy alone is enough for good seizure control others say that the best manage-

ment should include additional resection of epileptogenic zones adjacent to the tumor[26,28,36,39,40,44,62,119,120,125,126].

In Epilepsy-associated tumors it reaches a special meaning for the epileptogenicity and surgical strategies, the site of the lesion, *i.e.*, temporal, mesio-temporal (or limbic), temporo-lateral, paralimbic, extratemporal, eloquent areas[8,26,28,36,40,44,45,56,63,119,125,126].

Regarding limbic and paralimbic system, the role of hippocampus in the epilepsy network is pivotal since that could play a pivotal role in epileptogenesis even without obvious neuroradiological and pathological changes (*i.e.*, hippocampal sclerosis)[26,28,36,61,64,127].

The limbic system consists of the following elements, which are all directly or indirectly interconnected: the temporo-mesial structures (hippocampus, the parahippocampus,giryus) and the cingulate gyrus[58,60,61,128]. The paralimbic system is composed of 3 independent anatomical parts: the orbitofrontal cortex, the temporopolar cortex, and the insula[58,60,128]. The limbic system is connected *via* the entorhinal cortex and the uncinate fasciculus to the paralimbic system. In the setting of low-grade tumors associated with epilepsy WHO Grade Ⅱ gliomas are mainly found in the paralimbic system while glioneuronal tumors are found in the limbic system (temporomesial structures)[8,57].

LEAT are frequently associated with type Ⅰ or type Ⅱ a cortical dysplasia which, in contrast to focal cortical dysplasia type Ⅱb, are more difficult to identify with MRI[1,8,24,36,109,111,113]. It means that the anatomical structural lesion can be larger than what have been detected by MRI[110,113].

For this reason the target of the surgical resection should be the epileptogenic zone defined according to neuroradiological, clinical, neurophysiological and neuropsycological findings[40,129].

In case of LEAT located near or in eloquent area, the surgical approach is usually directed only to the anatomical structural lesion. Regarding the more frequent site of these tumors, *i.e.*, the temporal lobe, several approach have been used. The surgical strategy used in temporal lobe tumors includes lesionectomy, extended lesionectomy, tailored resection, anterior temporal lobectomy.

The majority of authors agree that lesionectomy alone provides the best seizure outcome results in LEAT located in the extratemporal and temporo-lateral site[40,42,44] while its results for temporomesial lesions are questionable[5,8,26,28,40]. Some authors suggested that the involvement of temporo-mesial regions may extend and make more complex the epileptogenic zone.

For this reason the amount of tissue removed in temporomesial surgeries is considered crucial to gain good postoperative results[5,8,60,62,63,65,125,130,131].

One important and persistent problem are the conflicting needs of the necessary extent of resection and the avoidance of neuropsychological deficits[126,131,132].

SEIZURE OUTCOME

Focal epilepsy associated with LEAT and particularly GG and DNT shows the best seizure outcome after surgery[5,18,28,36,92,95,119,132-134]. Some authors observed improvement of seizure outcome in young patients whereas others found no correlation with age at the time of surgery[4,28,38,132].

A recent literature meta-analysis about epileptogenic gangliogliomas in adult showed that an early surgical intervention of less than 3 years from the onset of seizure is significantly associated with improved seizure control[90].

Several studies reported that lesionectomy plus temporal tailored resection seems to offer the best results for seizure outcome[8,24,26,28,36,40]. Several authors insist that the the temporal pole has a pivotal role in epileptogenesis in temporomesial epilepsy[130,135,136].

The higher effectiveness of an extended resection beyond the LEAT might depend on the frequent association of this tumor type with other epileptogenic pathologies, such as the spectrum of cortical dysplasias that might represent the origin of a widespread epileptic network[8,24,34,36,68].

The new class FCD Type Ⅲb, which includes cases with abnormal cortical layering associated with a glial or glioneuronal tumor, has been introduced by the ILAE classification[34].

However in light of the frequent association of FCD Type Ⅱ with LEAT and the immunohistochemical evidence of a common pathogenesis linking LEAT and FCD Type Ⅱ[8,24,36,105], the possibility of creating a unifying class also for this kind of FCD should be considered.

With respect to oncological behavior, LEAT are usually indolent WHO Grade I lesions, although several reports have demonstrated that gangliogliomas may potentially have an evolving course and may demonstrate malignant transformation[33,40,70]. Pleomorphic xanthoastrocytoma can carry a higher risk of early recurrence when it is characterized by numerous mitoses and/or necrosis[137-139].

CONCLUSION

We believe that the adjective "long-term" included in the acronym LEAT could be prospectively confusing or misleading. Nowadays patients with LEAT are operated 5 years earlier compared to mid 1990s (mean of 7.4 years *vs* 12.9 years, respectively)[1,2].

The further increase in knowledge and a better recognition of these lesions among the scientific community (neurologists, epileptologists, neuropediatrics, neuroradiologists, epilepsy surgeons, neuropathologists) will lead to modify the present concept of "pharmacoresistance" *vs* a "tailored concept" of pharmacoresistance related to the underliyng pathology submitting many more patients to an early surgical treatment[107,132,140].

As a pathology-based approach to epilepsy surgery will be increasingly adopted[2,28,36,107,132,140,141] an early surgical treatment will become unavoidable.

In the near future this prototype of "surgically reme-

diable cause of epilepsy" will be properly operated early, irrespective of the concept of pharmacoresistance, making the adjective "long-term" obsolete and not appropriated.

An early surgical strategy can achieve various aims, namely to obtain a definite diagnosis, to contrast epilepsy progression (including psychosocial consequences and/or adverse effects of pharmacological treatment) and even to prevent the risk, present although uncommon, of tumor growth and malignant transformation. In addition, early surgery may reduce the risk of sudden unexplained death (SUDEP) or seizure-related injuries.

Such predictable future approach will modify the clinical history of these patients, and features of epilepsy as "chronic" or "long term", nowadays adopted in the definition of epilepsy-associated tumors, will loose sense. Neurophysiological aspects together with a proper histological and molecular characterization will become increasingly necessary for an accurate diagnosis of these epileptomas[25,34,85,142].

Therefore, what characterizes and makes up special for this group of tumors it is not the "chronic" or "long term" epilepsy history, but their pathological-biological features (*i.e.*, sharing of immunopositivity for CD34 and of BRAF (V600E) mutation[109,143].

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REVIEW

Pathways of fear and anxiety in dentistry: A review

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Abstract

The aim of this article was to analyze the theories underpinning dental fear, anxiety and phobias. To be included, articles must have been published between the years of 1949 and 2013 concerning fears and phobias within dentistry and/or psychiatry. Of 200 articles originally under review, 140 were included and reviewed by the authors.Five specific pathways relating to dental fear and anxiety were identified; Cognitive Conditioning, Informative, Visual Vicarious, Verbal Threat, and Parental. Eight currently accepted management techniques across all dental disciplines for dental fear and anxiety were identified. Further research is required to identify clinical diagnosis and treatment for fears originating from different pathways.

Key words: Dentistry; Fear and anxiety; Phobia; Origin; Therapies and management

Core tip: (1) 5 pathways to the origin of dental fear and anxiety have been identified in this review: Cognitive Conditioning, Informative, Visual Vicarious, Verbal Threat, and Parental; (2) Development of fear and anxiety may be unique for each individual, with patients often associating fear to a combination of factors (Pathways); and (3) Management of fear and anxiety should include an understanding of the origins of dental fear.

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INTRODUCTION

Odontophobia (dental fear) is a "unique phobia with special psychosomatic components that impact on the dental health of the odontophobic persons"[1]. For some individuals, dental fear may be so great that normal life is impaired. In these instances, the individual experiences fear or anxiety that is out of proportion to the actual danger present in the situation. This often leads to avoidance behavior, and clinically significant levels of distress or impaired functioning[2]. Such avoidance behavior is well known by any dentist who has treated patients with high levels of dental fear before. In Australia, people with higher levels of dental fear tend to avoid the dentist and have irregular attendance records, usually only seeking treatment when symptomatic[3,4]. This data is consistent with other studies that noted that, although patients booked appointments, they did not keep their appointment or prematurely cancelled their appointments out of

fear[5-12].

The incidence of dental fear and anxiety appears to be relatively consistent throughout the world, with some sub-groups reporting higher levels than others. An Australian study reported that 16.1% of individuals experienced high levels of dental fear, where adults between the ages of 40 and 64 years reported a higher incidence of dental fear, and females of any age were reportedly more afraid of the dentist than males were[4]. Of note, people from low socioeconomic status (SES) groups reported a generally higher level of dental fear than those individuals from high SES groups[4]. The reported incidence of high dental fear and anxiety was a little lower in an Icelandic study, at only 10%[11], but slightly higher in a Singaporean population, at 17.1%[12]. A cross-cultural study of Chinese and Danish patients reported moderate to high dental fear in 30% of Chinese and 15% of Danish participants[10]. In 2009, a study of dental fear prevalence in 1959 Netherlands reported 24.3% of the participants had moderate to high dental fear[13]. Dental fear studies on German populations have reported a mean Dental Anxiety Score (DAS) of 8.6[14] and a dental phobia incidence of 11%[15]. The highest prevalence of dental fear appears to be in Japan, where a study of 3041 students and adults reported that 42.1% had high dental fear[16].

The overall effect of dental fear and anxiety appears to be multifaceted, such that the individual not only avoids their dental appointments but also tends to have worse oral health[17]. The extent to which this is a causal relationship is unknown. An understanding of the factors underlying the etiology and maintenance of dental anxiety may assist dentists and researchers in developing interventions designed to reduce dental avoidance behaviors. In turn, this will contribute to improvements in oral health. Mehrstedt *et al*[18] (2004) noted that dental fears were negatively linked to quality of life with respect to psychological well-being, social functioning, and vitality. This finding indicates that the link between dental fear and perceived negative quality of life is multifaceted. Some early Scandinavian studies reported on the malicious circle of dental anxiety and fear, whereby fear and avoidance lead to premature cancellation of dental appointments and further worsening of oral health conditions[2,6,19,20]. A qualitative study by Moore *et al*[21] (2004) reported on the contributing role that embarrassment plays in dental phobia. Among other things, these researchers analyzed the social powerlessness associated with the embarrassment that arises from poor oral health. In this study, the authors concluded that patients may be so embarrassed by their poor oral health/hygiene that they avoid seeing the dentist out of fear of being reproached[1,21]. Understanding the extremely complex psychology of dental fear is essential in the prevention and treatment of dental anxiety, fear and phobias[21].

In order to understanding the extremely complex psychology of dental fear it is essential to understanding possible pathways of dental fear and anxiety. This study identified relevant studies using Medline Database (Medline/PubMed). The search covered the period 1900 to 2014, including only articles written in English. Search terms included "dental fear and anxiety," "cognitive," "informative," "verbal threat," "vicarious," "parental," and "origin of fear." A total of 300 references were retrieved from the database search. Only articles directly relating to the management, origin of fear, and dental fear theories were evaluated to understand the pathways of fear and anxiety in dentistry. Of the three hundred retrieved references, only 137 related to fear and anxiety in dentistry, however only 10 related specifically to origins of fear and anxiety in dentistry. The aim of this review is to highlight the possible pathways of fear and anxiety in dentistry and not to analysis the actual experience of fear and anxiety.

ETIOLOGY OF GENERAL FEAR AND ANXIETY

Processes known to contribute to the etiology of dental fear and phobia include a variety of genetic, behavioral, and cognitive factors. An individual's dental fear/phobia is likely to have been created by involving a multitude of factors.

Genetic vulnerability

Individuals with specific phobias, including odontophobia, may have inherited genetic vulnerability factors that predispose them to anxiety in general or certain phobias specifically. While individuals with dental phobia do not directly inherit the phobia itself, genetic vulnerability factors may interact with other etiological elements that cause the phobia[22,23]. Controversy over the reliability of phylogenetic origin of fear arises in relation to a study of 173 Swedish twins, which reported that whilst "phenotypic correlations were moderate," they were found to be counterintuitive to the electrophysical skin conductance response (SCR)[23]. In summary, it has been suggested that although genetics can predict some factors related to dental fear, it appears to be distally and not strongly related to the actual development of phobic symptom[24-26].

Negative affectivity/anxiety vulnerability

Negative affectivity refers to a vulnerability to experiencing negative emotional states. Negative affectivity appears to be a stable personality trait that predisposes individuals to a range of psychological disorders, including phobias[27]. The relationship between negative affectivity and dental phobia has not yet been established.

Preparedness

Through the process of natural selection, individuals who readily acquired fear and avoidance responses to genuinely dangerous situations (*e.g.*, dangerous animals, storms, heights, small spaces, *etc.*) have passed on this tendency to their progeny[28]. As such, the human species is "prepared" to more readily acquire fear reactions to stimuli that may have posed a genuine danger to our ancestors[28,29]. Dental

phobia may be part of an evolutionarily beneficial tendency to protect the body envelope from intrusion by foreign (non-nutritional) objects.

Cognitive conditioning (pavlovian)

Classical (or pavlovian) conditioning refers to the process by which a previously neutral stimulus acquires the ability to directly elicit a response through pairing this stimulus with another unconditioned stimulus (US) that elicits the same response[30-33]. For example, an individual who experiences a painful procedure (and the unconditioned response of anxiety/fear) during a dental visit may acquire a conditioned association between the dentist (the conditioned stimulus) and anxiety/fear (the conditioned response)[34-37]. Re-presentation of the conditioned stimulus (the dentist or related stimuli) is then able to elicit the conditioned response of anxiety during the patient's next dental consultation.

Operant conditioning

Operant conditioning refers to a process whereby the frequency of a particular behavior ("operant") is modified through the consequences that follow the behavior. Certain behaviors may be "reinforced" (*i.e.*, increased in frequency) through their association with positive consequences ("positive reinforcement") or through the removal of negative consequences ("negative reinforcement")[30,34,35,38,39]. Alternatively, behaviors may be "punished" (*i.e.*, reduced in frequency) if they lead to negative consequences ("positive punishment") or the removal of positive consequences ("negative punishment")[38]. For phobias, the process of positive punishment (*e.g.*, pain and anxiety that occurs during a visit to the dentist) and negative reinforcement (*e.g.*, the reduction in anxiety that results when the individual avoids the dentist) are thought to be most important, and these comprise Mowrer's two-factor model of phobia acquisition and maintenance[40].

Vicarious

In addition to direct contributors to phobia acquisition, Rachman[41] (1978) proposes that individuals may also acquire phobic responses indirectly. One such pathway has been called vicarious experience or vicarious conditioning. In vicarious conditioning, the individual acquires a fear response through seeing the fearful experience of others. In dental phobia, for example, a child who observes a fear response of a parent attending the dentist may learn indirectly that the situation poses a significant threat.

Verbal threat

Rachman[36] (1977) proposed a second indirect pathway to phobia acquisition referred to as "verbal transmission". In this process, the individual acquires a fear or phobia through learning about the dangerousness of a situation from others without observing it directly[36]. In dental phobia, for example, an individual may hear stories from others about traumatic or painful experiences that they have had during dental treatment, which may lead to a learned fear of dental procedures[42].

Cognitive content

There are a range of cognitions that have been identified as important in the acquisition and maintenance of anxiety disorders, including specific phobias. These include a set of ideas about the probability (*e.g.*, "If I go to the dentist it will definitely be painful") and severity (*e.g.*, "If I go to the dentist the pain will be excruciating") of negative outcomes[43]. Additionally, individuals may hold beliefs about their inability to cope in the face of an aversive outcome (*e.g.*, "If I am in pain at the dentist, it will be unbearable")[44].

Cognitive biases

In addition to the content of cognition, phobias are associated with biases in the process of cognition[43]. For example, individuals with anxiety disorders such as phobias are known to have memory biases in which memories of threat-consistent experiences and information are more readily retrieved[45]. Although the link between cognitive bias and dental fear and anxiety is plausible, no research has yet been done to confirm this.

CURRENT KNOWLEDGE OF DENTAL FEAR: WHAT WE KNOW RIGHT NOW

Current literature on dental fear is limited relative to other fields. Specifically, most of our understanding surrounding dental fear is based on results from two meta-analyses; one of which focuses on adults, while the other on children and adolescents.

In a meta-analysis of 32 articles on dental behavior management problems, Klingberg *et al*[46] (2007) reported that children and adolescents were expected to experience mild fear and anxiety. This fear and anxiety only becomes a concern if it is "disproportionate to the actual threat and daily functioning becomes impaired", a definition very similar to the DSM-IV. However, this research also noted that the third criterion for dental phobia (recognition that the fear is unreasonable or excessive) does not always apply to children. This is a reasonable argument, as coping with pain and anxiety requires a high level of cognitive function and self-control that a young child might not have yet developed. However, one must attempt to separate general fearfulness (an anxiety-related personality trait) from a specific fear because both are capable of presenting as an acute fear reaction (*e.g.*, screaming at the sight of a drill). This distinction can be difficult to make if the parent-child relationship is synergistically inflating the dental fear. Research demonstrates that the dental fear of a child who is 8 years or younger is significantly related to the dental fear of the parent[47]. However, in children older than 8, the relationship is less clear. In addition, it was noted that girls presented as more anxious and harder to manage than boys, sup-

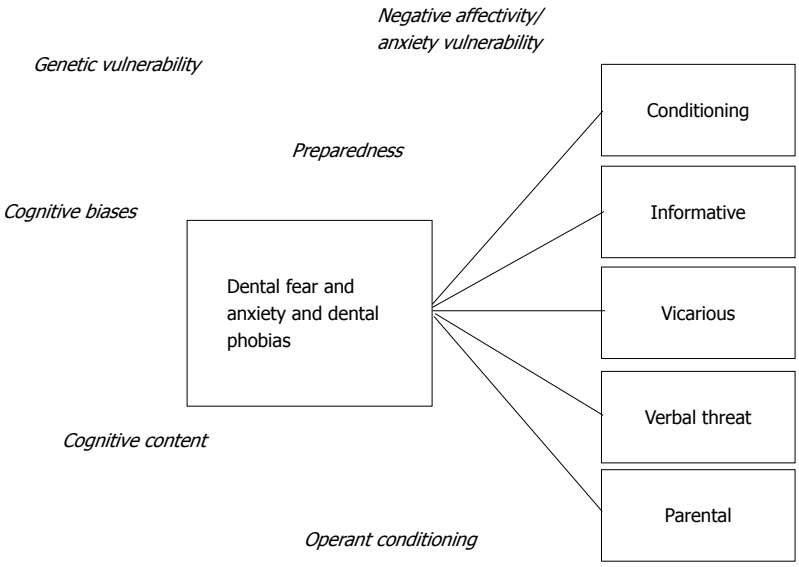

Figure 1 Pathways of fear in dentistry with background influences.

porting the current accepted relationship between anxiety disorders and gender in children and adolescents[48]. However, particular fears changed as the child grew older, such that one-year-old had separation anxiety but primary school children had more social anxieties, demonstrating a positive development of metacognition. Also, younger children were more likely to have more fears of higher intensity. However, there is inconclusive evidence regarding the origin of fear among children and adolescents due to the gap in the literature examining this cohort. In their review, Klingberg *et al* (2007) did, however, agree on 3 distinct, yet commonly occurring causes for dental fear in children (not including neuropsychiatric disorders): (1) Some children's past "negative experiences with dental care" was the origin of their dental behavior management problems; (2) Other children were "genetically prone to react with fear…to threatening situations"; and (3) Other children still reacted to frustrating demands (*e.g.*, sitting still) with anger[46].

The first represents direct trauma from treatment[36], while the second and third are officially undefined at present and require further investigation. It must be noted that parental dental fear has an effect on the child' s dental fear[47,49]. Making it an important part of the conceptualization of an individual's dental phobia.

With regard to adults, it is generally accepted that the patient developed fear either due to personal trauma from a dental treatment or because of some form of psychological disorder or constitutional vulnerability. Yet, few studies analyze the actual pathway or origin of fear adults experience with regard to dental fear. However, it is possible that some of these origins may apply directly to dental fear[50] (Figure 1). Originally Watson *et al*[33] (1920) and Rachman[41] (1978) purported that specific fears were condition-based, vicarious, or based on information learning. Between the 1920s and 1970s, these theories dominated the discipline of fear and anxiety management and diagnosis. In 1970, Seligman proposed that mankind is prepared by evolution to associate certain situations (previously encountered by ancestors) with particular outcomes, and thus the mind reacts to these situations by instigating fear (See Figure 1: Preparedness framework)[51]. In 2001, Mineka *et al*[28,52] suggested that the amygdala and hippocampus were responsible creating generalized fear responses. Analogous to this and supporting Seligman's theory, Poulton *et al*[53,54] (2002) posited that evolutionarily associated fears can manifest without a stimulus. Among these theories, the associative and non-associative theories are the most distinctive. Menzies *et al*[55,56] (1993a) first described the associative theory in relation to water phobia, where fears occur in response to a bad experience (CS), while non-associative fears are innate (US). In addition, Muris *et al*[57] posited that parental modeling contributes to the fearfulness found in children. Here, the trait anxiety was related to that of both parents (Mother: $r = 0.34$, $P < 0.05$, Father: $r = 0.31$, $P < 0.05$), but the act of being fearful was only related to mother's fearfulness ($r = 0.56$, $P < 0.001$)[57]. Klingberg *et al*[58] also supported the notion of maternal dental fear impacting the development of dental fear in children.

Of these theories, there are 5 pathways that are thought to specifically relate to dental fear and anxiety: Cognitive Conditioning, Vicarious, Verbal Threat, Informative, and Parental (Figure 1). These five pathways are discussed further in this article but it is important to note that a single or a combination of background factors disused in the etiology of general fear and anxiety may affect these pathways.

Conditioning pathway

Conditioning is a process where the participant learns through personal experience that the event or stimulus heralds a detrimental outcome[50,59]. Pioneers in early conditioning research Watson *et al*[60] (1917) who theorized that in infancy there are limited emotional reaction patterns (*e.g.*, fear, rage, love) and that there must be some stimuli which are associated with these. Watson *et al*[33] (1920) then performed experimental work on an infant,

analyzing directly conditioned emotional responses. Their results showed that the non-fear-inducing stimuli elicited a fearful emotional response when the fear-inducing and non-fear-inducing stimuli were shown together, and when the non-fear-inducing stimuli was shown on its own later[33]. In 1927, Pavlov[32] published his seminal paper on "Conditioned Reflexes," which perhaps represents the first in-depth and detailed experiment on the development of conditioning. Pavlov[32] identified that animals can learn to associate a conditioned stimuli with a new non-conditioned stimuli so that the non-conditioned stimuli causes a conditioned response. Here, the animals (dogs) began to associate food and salivating with the sound of a bell. Thus, anytime the bell sounded, the dogs salivated[32]. In a similar attempt to replicate physiological responses during fear, Rachman[41] (1978) then successfully demonstrated that physiological responses, such as sweating and increased heart rate, occur when individuals experience fear. Such responses are evident in odontophobic patients, where heart rate, breathing, and sweating all increase due to fear associated with dental environments and dental stimuli[19,61-63]. In addition, many individuals report painful past experiences being the cause for their subsequent dental fear[44,64-66]. Researchers[67] have indeed found a "strong direct relationship between severity of trauma-related symptomatology and severity of dental anxiety where the shared variance was 38%"[67]. Thus, it can be proposed that the majority of dental fears are reactions to stressful experiences that provoke anxiety in the individual[36,68-70]. In summary, the conditioning pathway appears to be the most commonly utilized pathway by patients.

Informative pathway

The informative pathway is another indirect pathway for fear acquisition, which does not require the presence of an unconditioned stimulus. As far back as 1977, Rachman discussed the relevance of the informative pathway in so much as child-rearing involved information giving[36]. Rachman[36] noted that the instructional process of child rearing may lead to biases for commonly encountered fears. Such a dynamic could help explain childhood dental anxiety, where children learn to fear the dental environment from dental phobic elders, negative connotations advertised by media (*e.g.,* television, movies), and friends with personal negative experiences.

Vicarious pathway

The vicarious pathway is an indirect pathway for fear acquisition that does not require the presence of an unconditioned stimulus. It has been acknowledged in the literature that people with extreme dental fear avoid the dentist[3,4,17,33,71-78]. In a recent Australian study using Armfield's Index of Dental Anxiety and Fear (IDAF), it was found that participants who indicated extreme dental fear were marginally more likely not to undertake an oral examination, here females exhibited significantly higher dental fear than males[4,71]. Whether this fear is purely conditioned or vicarious is not yet fully understood[76]. Conceivably, one of the most renowned contributions to the theory of "vicarious conditioning in phobia acquisition"[50] was by a pair of researchers[38,52,79] whose experiments provided convincing evidence that fear can be learned vicariously[36,69,80]. By utilizing this vicarious pathway, it is plausible to suggest that vicarious learning could be contributing to pediatric fears, whereby expressions of fear by elders at the dentist in front of children leads to fear acquisition in the children[81,82].

Verbal threat pathway

The verbal threat pathway presents another indirect pathway for fear acquisition that does not require the presence of an unconditioned stimulus. To explain the origin of a fear that is not seen or experienced, it is essential to understand the "*emotion*" of fear. Research[83] has suggested that emotions arise because of three factors: verbal cognition, behavior changes, and physiological states. This "*emotion*" is known as the "tripartite," and appears to govern onset and origin of fears generated by the verbal threat pathway[83-87]. Many articles examining the effects that "word of mouth" information has upon children and acquisition of fear[81,82,84-86,88-97] note that children become fearful of a stimulus or situation when they hear or read that it may be dangerous. To control for bias, all studies were done on medically healthy children, aged 6-13 years. The majority of participants (88.9%) demonstrated that self-reported fears increase as children were given violent/dangerous/threatening information about a particular stimulus, irrespective of its actual threat[85,86,92-94]. Simultaneously, it has been found that giving positive information results in a decrease in children's self-reported fear[89,91]. Similar research on children ages 7-9 years found that when given verbal information about a "monster, "children's fear-beliefs changed. However, these fear-beliefs only changed when information came from an adult[96]. In short, one interpretation of the verbal threat pathway is that fear is induced when an authority figure threatens an individual with a painful experience. In the case of dental fear, painful and/or negative experiences are linked to dental visits. Although perhaps within strict psychological terminology the informative and verbal threat pathways are similar. Within odontophobia the two pathways differ in that the verbal threat pathway occurs when a "visit to the dentist" is literally used as a form of punishment for bad behavior. This does not occur in the informative pathway.

Parental pathway

The parental modeling pathway presents another indirect pathway for fear acquisition that does not require an US. The concept of parental modeling is supported by research[69] demonstrating that in a sample of 40 children between the ages of 9 and 12 years, children's fear was positively related to their mother's dental fear. Specifically, mothers who expressed heightened levels of fear in front of their children were more likely to have fearful children.

Conversely, mothers who did not frequently express fear had less fearful children[69]. These findings are consistent with another study showing that most adults attributed the origin of their fears to informative and vicarious factors occurring in childhood (56% and 39%, respectively) more so than to cognitive model events (37%)[84]. Given that the majority of heightened levels of fear in some children was a consequence of an amalgamation of different learning dynamics[69], it has been suggested that "fear is more likely to develop as a result of synergistic effects of various sources or origins"[56]. However, one must note that any relationship between parent and child fears may also be due to the informative or vicarious pathways because they are all linked in some way. Again, strict psychological terminology may not necessarily differentiate between the parental and vicarious pathways. However within odontophobia individuals utilizing the parental pathway had their sole influence of odontophobia from their parents' expression of fear, whereas the vicarious pathway is multifaceted. Further investigation is needed to identify criteria for each pathway's application.

MEASUREMENT INSTRUMENTS AND DIAGNOSTIC CATEGORIES OF DENTAL FEAR AND ANXIETY

Measures of dental anxiety (Pre-1990)

The first widely accepted questionnaire for assessing dental fear was the Phobic Origins Questionnaire (POQ). Out of the 10 items, the first 9 required the participant to make a binary Yes/No response[98,99]. Following the POQ, a 16-item self-report questionnaire referred to as the Origins Questionnaire (OQ)[56,100] became popular. This measure also examined individuals' history in relation to their phobia[55,56]. However, as several studies have indicated[56,101-103], the POQ is inherently biased towards conditioning models. It was found that the POQ indicated conditioning was the primary origin for fear 56%-78% of the time, while the vicarious pathway accounted for 17%-42%[104]. Additionally, given that the control group for this research[99] consisted of only analogue cases of mild and low level fear by different researchers[77,105-107], it cannot be confirmed that this research represents the general populations' origins of fear. Numerous other researchers have criticized the POQ, noting that the authors wrongly systematized frightening stimuli to relate to the cognitive model origin, even though no unconditioned stimulus was described by participants[55,56,108,109]. Consequently, the construct validity and convergent validity of the POQ was found to be very poor[55,56,100,101,103,110,111].

Measures of dental anxiety (Post 1990)

As dental fear can be difficult to define and measure effectively[103,109], research began to create a more practical, reliable, and theoretically efficacious dental fear measurement. Research found that the Index of Dental Anxiety and Fear (IDAF-4C+), developed by Jason Armfield presented strong statistically significant correlations with previous measures of dental fear (Corah's DAS, 1969). Armfield's reasoning for creating a new dental fear scale was due to problems with existing scales such as Kleinknecht's Dental Fear Survey (DFS, 1973), Stouthard's Dental Anxiety Inventory Short-Form (DAI-S, 1993), the Modified Dental Anxiety Scale (MDAS, 1995), and the Hierarchical Anxiety Questionnaire (HAQ, 1999). Problems associated with these measures were that they were too long, measured fear-related stimuli rather than fear itself, and had poor construct validity[71,77,112,113].

Consisting of 3 modules, each with 8 items, the IDAF-4C+ analyzes emotional, behavioral, physiological, and cognitive responses related to dental fear[66,113]. Each module uses a Likert scale ranging from 1-5, where 1 represents "strongly disagree" and 5 represents "strongly agree." Utilizing an exploratory analysis, "all items showed good internal consistency (Cronbach's alpha = 0.94) and test-retest reliability at 4 mo review (r = 0.82)"[71,114]. With regard to phobia diagnoses, positive results were found with regard to the convergent and predictive validity of the IDAF-4C+ when compared to Corah's DAS, Eta^2 = 0.154 and 0.060, respectively[71].

Diagnostic categories of dental fear

Individuals who are classified as "dentally anxious," tend not to have qualities that can be catalogued. As such, they differ in their origin of fear, specific fear stimulus, age of onset, as well as the bodily reactions and psychological reactions that manifest in response to fear-related stimuli. The etiology of dental fear is wide-ranging and can be attributed to personal traumatic experiences (conditioning)[38], threats of dental visits as punishment (verbal threat pathway)[86,93], and fear through observing pain in loved ones and others (vicarious pathway) to name a few[50,99,115,116]. Moreover, at times, dental fear has been shown to be part of a larger "set" of fears such as arachnophobia and claustrophobia, and fears of mutilation and suffocation. Consequently, there has been debate on whether dental anxiety is a "simple" CS, or a component of a "set" of fears and mood or anxiety disorders[117]. Previous and well documented research has described these two variations of dental fear as exogenous and endogenous[118].

A group of researchers, well known for their clinical experience, developed a richer, more detailed classification system for dental fear. Their system, known as the Seattle System, mirrored the origin and the main stimuli of fear surrounding dental anxiety and phobias[116]. Essentially, the Seattle System can be used to classify individuals with respect to the severity of the psychological phobia relative to dentistry and the dentist as a person, based on a range of mean scores that represent different levels of dental fear. These mean scores have been applied to a number of questionnaires [*i.e.*, DAS, Fear Survey Schedule II (FSSII), Spielberger Trait Anxiety Index (STA), Anxiety Sensitivity Index (ASI), Emotional Control Questionnaire (ECQ), General Health Question-

naire (GHQ), Fear of Pain Scale (FPS), and Mutilation Questionnaire (MQ)]. The Seattle System consists of four diagnostic elements: (1) simple CS of specific dental stimuli; (2) anxiety about somatic reactions during dental treatment; (3) patients with a generalized anxiety state and multi-phobic symptoms; and (4) distrust of dental personnel[116,119]. Despite the fact that the classification was originally designed for pragmatic academic purposes, it has shown to hold some evidence of psychologically valid identifications of dental anxiety subtypes[19]. Of note is the qualitative evaluation component of the Seattle System, which consists of in-depth interviews that give a more thorough understanding of the true multiphobic nature that dental fear can present with[19]. Indeed, subjects with type 4 Seattle fear were further split into 3 subgroups, which met the criteria for distinct uniqueness, internal consistency, and distinct response to treatment type as proposed by earlier researchers[120].

Roughly comparable results were reported three years later utilizing the DSM-III-TR criteria for simple dental phobia (code 300.29-Specific phobia)[121]. However, although the results did not support the theory that the Seattle System corresponds to the DSM-III-TR, as proposed three years earlier[19], the researchers proposed that dentally anxious subjects should be calibrated for fear using a distinct method that differs from that for psychiatric mood and personality disorders[121]. Then, just before the turn of the century, newly published research brought to light some intriguing facts regarding the Seattle System[119]. Here, it was proposed that the Seattle System was valid from a psychological perspective in addition to being a well-rounded tool for clinical diagnosis (Table 1). Accordingly, they discovered that some participants in the older age brackets were of type 3 fear (Seattle System), indicating that those with simple phobias are able to recover in time, while those individuals with more complex multiphasic conditions may require psychological treatment[119].

CURRENT MANAGEMENT TECHNIQUES FOR DENTAL FEAR AND ANXIETY (CBT)

With regard to treatment of dental fear and anxiety, there a number of possible avenues to explore with patients, including pre-treatment anxiety questionnaires, cognitive behavioral therapy (CBT), relaxation therapy, computer-assisted relaxation learning (CARL), hypnotherapy (HT), group therapy (GT), individual systematic desensitization (ISD), pharmacological, flooding (implosion), and swallowing relaxation. These forms of treatment are essentially a form of counter conditioning to reverse the fear into a state of acceptance and calm.

Pre-treatment anxiety questionnaires

To date, only one study exists as to general dentists' use of pre-treatment anxiety questionnaires to assess patient anxiety before treatment. A study of United Kingdom dentists reported that only 20% of the dentists surveyed used adult anxiety questionnaires, and only 17% formally assessed children's levels of fear and anxiety[122]. Interestingly the study reported that when treating adults, male dentist used pre-treatment fear surveys more often than female dentist ($P < 0.05$)[122]. The authors believe that these pre-treatment surveys can help enhance patient care; however it would be interesting to evaluate the current utilization rate of these anxiety surveys and methods to encourage this practice.

Individual systematic desensitization and group therapy

Individual systematic desensitization (ISD) is a behavioral therapy whereby individuals are gradually exposed or incrementally exposed to fearful stimuli. In this process, the individual must first identify and accept the fear-related stimulus; second, the individual must learn to employ a relaxation or coping technique; and finally, the individual must utilize the learned relaxation or coping strategy to react and overcome the fearful stimulus. In 2002, Moore *et al*[123] compared GT and ISD (as well as HT) and found that after 3 years, 65.5% of patients' with ISD and 69.6% with GT maintained dental appointments (although these results were not significant). In this work, the ISD was a combination of muscle relaxation therapy and video reel exposures (looped) of threatening dental situations and instruments with intermittent tension awareness training and breath control lessons. GT involved groups of patients meeting for seven 2-h sessions led by a dentist, dental assistant, and successful former patient. Video desensitization reels were also played and a final demonstration of injection and drilling was performed at the last session. Unfortunately, Moore *et al*[123] (2002) did not identify the origin of fear for the participants. Thus, the current results cannot be extrapolated to the pathways and further research is needed.

Flooding/implosion

Flooding is a form of desensitization for treating phobias when the patient has a directly conditioned origin of fear (Origin 2). In flooding therapy, the patient is subjected to repeated exposure of fear-inducing stimuli until they no longer show a fear response, causing termination of the CR[124]. Implosion is used for either indirect conditioned or non-conditioned origins of fear (Origins 1 and 3) that may be imagined. However, the technique of flooding has not been examined in the literature since Mathews *et al*[125] in 1977. In this work, Mathews *et al*[126] report that among subjects who attended 2 or more flooding sessions, 48% successfully completed dental treatment 2 mo later. No further investigations appear to have been performed on this technique; this might be due to the highly anxiety-inducing nature of the treatment.

Cognitive behavioral therapy

Cognitive behavioral therapy (CBT) is a psychotherapeutic approach to address dysfunctional emotions and negative behaviors and cognitions using a series of goal-oriented sessions. Davies *et al*[126] (2011) found that of 21

Table 1 Seattle system diagnostic criteria for dental phobia

Fear type	Diagnostic Item	Classification of fear
Type 1	Fear of dental procedures	Simple conditioned phobia
Type 2	Fear of fainting, panic attack, heart attack	Fear of catastrophe
Type 3	Nervous person in general	Generalized anxiety
Type 4	Distrust of dentists	Fear of dentists
Subclass a		→High fear of dental procedures
Subclass b		→Generally anxious
Subclass c		→Fearful of dental catastrophes

patients offered CBT to overcome their dental fear as opposed to using sedation, 90% continued to be able to attend dental appointments without sedation ten years later. Current research appears to support CBT and relaxation therapy for treatment of directly conditioned fears (Origin 2)[127,128].

Relaxation therapy

Relaxation therapy is a diverse set of practices aimed at eliciting a relaxation response, including a reduction in overall physical arousal symptoms. The phobic individual implements a particular mental relaxation technique (*e.g.*, slow breathing, counting, relaxation swallowing) to reduce stress. ten Berge *et al*[129] (2001) reported that parents play a more secondary role in treatment of child dental fear and anxiety. Results seem to suggest that CBT is more effective but should be combined with parental guidance in treatment of pediatric dental fear. Extrapolating this data, a combination of CBT and relaxation guidance may provide effective treatment of parental modeling dental fears (Origin 1).

Computer-assisted relaxation learning

A recent development in the treatment of dental fear, computer-assisted relaxation learning (CARL) is a self-paced treatment for dental phobic individuals for treating needle phobia. The program begins by introducing its purpose, followed by activities and videos on how to cope with their fear. The program is based on the theory of systematic desensitization and in a recent study in 2013, researchers compared CARL to information pamphlets (control) in a block randomized study[130]. The authors reported that CARL significantly reduced self-reported general and injection-specific dental anxiety ($P < 0.001$)[131]. After the intervention, twice as many CARL participants (35.3%) *vs* controls (17.6%) were comfortable enough to receive an injection though not significant (12 of 34)[131]. Participants' origins of fear were not assessed, thus it cannot currently be determined which pathways were involved, and further research is required. However, as CARL is self-paced, it may perhaps aid in treating patients who wish to learn to cope without therapists, thereby improving access to oral health care.

Hypnotherapy

Perhaps one of the least understood treatments for dental fear is hypnotherapy (HT). HT attempts to create a state of unconscious change, whereby the individual forms new responses, attitudes, and behaviors to previously feared stimuli. Few studies have analyzed the clinical effectiveness of hypnotherapy. In 1995, research reported that when compared to psychophysiological therapies such as CBT, HT did not significantly reduce dental fear[132]. Researchers purported that this was because some people were put off by the concept of hypnotherapy and were not fully receptive to the therapy[132]. Some years later, Moore *et al*[123] (2002) found that although 54.5% of HT patients were able to maintain regular dental appointments, at 3 years post treatment, there was no difference between the HT, GT, or ISD groups.

Pharmacological

The use of nitrous oxide (NO) and benzodiazepines in dentistry has long been employed to reduce anxiety. NO has often been compared to the effectiveness of CBT and relaxation therapies. For example, Willumsen *et al*[133] (2001) reported no significant differences between NO and CBT or applied relaxation therapy. They suggested that in the short term, either treatment was effective. Interestingly the study reported a 95% of participants attended rate a year later, with the greatest reduction in dental fear observed in the relaxation therapy group[130]. While all groups reported normal levels of dental fear (as per Corah's DAS) one year later[130], analysis of benzodiazepines when combined with ISD did not reduce overall therapy time and was not advantageous for treating injection phobia[134]. The studies did note that the results might have been skewed by the fact that each participant's dental fear might have different origins. Thus, research is required to determine whether certain origins of fear and pathways are more receptive to pharmacological agents than others are.

CONCLUSION

The present article has highlighted the possible types of dental fear, their origins in dentistry and current knowledge on management of patient with fear and anxiety. There is, however, a lack of knowledge of the effects of demographics, causal factors, ethnicity, and treatment modalities relative to the origin and pathways of fear in dentistry. Understanding, the origin of a patient's fears and anxiety could help enhance patient management and care.

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MINIREVIEWS

Squamous cell carcinoma of the scrotum: A look beyond the chimneystacks

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Abstract

Despite the low incidence, squamous cell carcinoma (SCC) remains the most common scrotal malignancy with a propensity for recurrence and metastasis. In recent years there has been a significant change in the epidemiology of scrotal SCC. Surgery is the mainstay of treatment for resectable disease. Sentinel lymph node dissection adapted from experience with penile SCC can reduce the morbidity of routine lymph node dissection. Emerging treatments for advanced and metastatic SCC are at the cusp of significantly changing management of this disease. We have performed a comprehensive review of scrotal SCC with a focus on these topics.

Key words: Squamous cell carcinoma; Genital cancer; Scrotal cancer

Core tip: Scrotal squamous cell carcinoma (SCC) although rare, represents one of the most common forms of scrotal malignancy. The epidemiology of SCC has changed over time and iatrogenic conditions (psoralens and ultraviolet A radiation, immunosuppression, *etc.*) and human papilloma virus infection play a significant role as associated conditions. Surgery is the cornerstone of treatment and primary excision with a risk stratified approach for staging and treatment of regional lymph node is advisable. Sentinel lymph node biopsy can mitigate the morbidities of unwarranted inguinal lymph node dissection in selected cases. For locally advanced and metastatic disease palliative chemotherapy is advocated. Targeted therapies might hold promise for management of advanced SCC.

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INTRODUCTION

Squamous cell carcinoma (SCC) is the most common scrotal malignancy[1,2]. Despite awareness and removal of occupational carcinogens over the last century, after initial reduction in incidence, scrotal SCC has maintained a steady incidence rate. Due to significant associated morbidity and mortality it remains an important urogenital malignancy for the urologist. Our aim was to review recent published literature on scrotal SCC and highlight changing epidemiology as well as emerging therapies.

HISTORICAL BACKGROUND

The earliest accounts of scrotal SCC date back to the Persian nomads who used to transport pots of burning coal between their legs to keep warm as they travelled[3]. The first clinical descriptions of cases occurring were by Bassius and Treyling in the mid 1700s, with Treyling describing a case in a Cavalryman[4]. Sir Percival Potts in 1775 was the first to link the chronic lodgment of soot in the rugal folds of the scrotum occurring in chimney sweeps to development of scrotal SCC[5-7]. It hence became known as the first described occupational disease. The active carcinogen discovered later was 3,4-benzpyrene. Occupational scrotal SCC was also later described in association with other occupations with chronic carcinogen exposure including cotton mule spinners, paraffin and tar workers, creosote workers, shale oil workers, lathe workers, pitch workers and machine tool setters and operators[4,8-12]. More recently it has been described in car mechanics, car and airplane manufacture, gas workers, engineers, steel manufacture and aluminum workers[11,13-15]. The majority of occupationally related scrotal SCC can be attributed to exposure to carcinogenic polycyclic aromatic hydrocarbons[10].

EPIDEMIOLOGY

In order to assess recent trends in the epidemiology of scrotal SCC, we examined all clinical studies published on scrotal SCC since the year 2000.

There were six case series published including two Surveillance Epidemiology, and End Results (SEER) based analyses, one Netherlands Cancer Registry (NCR) based analysis, one prospective multi-institutional study and two retrospective studies[1,2,16-19].

Studies in the mid-to-late 1900s reported that scrotal SCC accounting for the majority (80%-100%) of all scrotal malignancies but in more recent reports it only accounts for one-third of all scrotal malignancies[1,2,16,20,21]. However scrotal SCC still remains the most common scrotal malignancy[1,2,16]. Other scrotal malignancies include extramammary Paget's disease (EMPD), sarcoma, basal cell carcinoma, melanoma, Bowen's disease (SCCIS) and adnexal skin tumors. Median age at diagnosis ranges from 52-57 years[1,18,19]. Most cases occur in Caucasian men followed by Black and Asian men and other ethnicities.

Verhoeven *et al*[1] reported the age-standardized 5-year incidence rate of all histologic types of scrotal cancer in the Netherlands and this varied between 0.9 and 1.8 per 1000000 male person-years from 1986 to 2006 with no statistically significant change over time[1]. Age-standardized incidence rate of scrotal SCC varied between 0.34 and 0.44 per 1000000 male person-years from 1986 to 2006. Over a similar time period Wright *et al*[2] reported on the age-adjusted incidence rate of scrotal cancer in the United states which increased from 0.49 per 1000000 persons in 1973 to 0.95 per 1000000 persons in 2002. While specific incidence rate of scrotal SCC was not provided they did report no change in incidence rates by histologic type[2]. The incidence reported from the Connecticut Tumor registry data from 1935 to 1979 showed stable incidence rates of all scrotal malignancies and epithelial scrotal malignancies[22]. It has been speculated that the reason for this sustained incidence despite occupation carcinogen avoidance has been the emergence of new risk factors such as phototherapy for the treatment of skin diseases and human papilloma virus (HPV).

Johnson *et al*[16] reported on the largest SEER series of scrotal squamous cell carcinoma with 269 patients focusing on histologic subtypes. They categorized scrotal SCC, melanoma and adnexal skin tumors as high-risk scrotal cancer and scrotal basal cell carcinoma, EMPD and sarcoma as low-risk based on median overall survival of 118 mo for the high-risk group and 166 mo for the low-risk group[16]. Survival for scrotal SCC was 115 mo (range 97-133), which was the second lowest with lowest being adnexal skin tumors with median overall survival of 114 mo[16]. Wright *et al*[2] reported statistically significant worse survival for those with SCC than for those with other histologic types. SCC comprised 35% of all scrotal tumors in whites compared to 69% in blacks[2]. Dutch researchers reported 77% 5-year survival for scrotal SCC[1].

In early 1990s, Goldolf *et al*[23] reported that the incidence of scrotal SCC despite increase in the rates of UV exposure through sunbeds and sunlamps has not changed. However psoralens and ultraviolet A radiation (PUVA) used for the treatment of psoriasis and other inflammatory skin diseases has been implicated with the development of scrotal SCC[24,25]. In 1990 Stern reported on a prospective 12.3 year study in 892 men who had undergone ultraviolet radiation as part of their psoriasis treatment, out of which 14 developed genital tumors including 5 patients who developed 9 invasive scrotal SCC and one scrotal SCC in situ (SCCIS)[26]. They found that patients with high dose PUVA had 286 times the risk of the general population to develop invasive genital SCC, low dose PUVA had 16.3 times the risk and high dose UVB was associated with 4.6 times elevation of the risk[26]. Authors recommended genital protection for men undergoing UV radiation for treatment of skin diseases.

Increasing incidence of oropharyngeal SCC has been attributed to increasing prevalence of oral mucosal HPV[27,28]. HPV viral oncoproteins E5, E6 and E7 have an important role in carcinogenesis with p53 tumor suppressor gene and Rb oncogene being the major targets[29]. HPV infection in scrotal SCC has only been reported in a few case reports or small series[18,30-33]. Andrews *et al*[32] reported a total of 6 (42.9%) out of 14 cases were associated with HPV.

Matoso *et al*[18] reported on 29 patients with scrotal SCC and found high-risk HPV in 7 cases (24.1%) assessed by *in-situ* hybridization. These authors also reported p16 positivity and elevated Ki67 in HPV positive scrotal SCC. These cases were also more likely to display a basaloid or

Table 1 Risk factors associated with scrotal squamous cell carcinoma

Occupations
Chimney sweepers, tar and paraffin workers, occupations with exposure to mineral and cutting oils, printing, metal working, car and aeroplane manufacture, car mechanics, commercial printing, aluminum worker, shale oil workers, pitch workers, engineering, steel production, cavalrymen
Carcinogenic metals
Arsenic, nickel, chromium
Chronic mechanical irritation
Chronic inflammatory states
Chronic lymphedema, infective and surgical scars
Lifestyle
Poor personal hygiene, smoking
Viruses
HPV
Ionizing Radiation
Iatrogenic
Coal tar, PUVA, radiotherapy, nitrogen mustard, Fowler's solution
Immunosuppression
Acquired and inherited immunodeficiency, post transplant immunosuppression

HPV: Human papilloma virus; PUVA: Psoralens and ultraviolet A radiation.

warty morphology. They suggested p16 stain to be used for screening for HPV infection with addition of Ki67 in cases with equivocal p16. If indeed the true proportion of HPV associated scrotal SCC lies between 24%-42% as in these small series, it has important implications for preventive therapy with the availability of HPV vaccines.

Chronic mechanical irritation has been associated with scrotal SCC. Long-term rubber urinal use[34], topical nitrogen mustard[35] and coal tar[36] have been reported to be associated with scrotal SCC. Initially scrotal SCC was thought to be uncommon among non-Caucasian ethnicities however subsequent reports in Africans, African Americans and other ethnicities including Chinese refuted this hypothesis[37,38].

Both preceding and subsequent increased malignancy risk has been described in patients with scrotal SCC[39]. Verhoeven reported 18% of patients with scrotal malignancy developed one or more tumors after the scrotal tumor with lung cancer, skin SCC and second scrotal tumor being the most common second malignancy[1].

DIAGNOSIS

The most common presentation of scrotal SCC is of an erythematous scrotal nodule or plaque[40]. Ulceration and pruritus often accompany the lesion. It occurs most commonly in the left scrotum, lower and anterior areas[40,41]. It can uncommonly present as abscess or ulcer[42]. The main differential diagnoses are extramammary Paget's disease, verrucous carcinoma and bowenoid papulosis[43-46]. Pigmented scrotal SCC and scrotal SCCIS have been rarely reported[38,47]. Multiple scrotal SCCs in the same patient have often been described[26,48]. Table 1 lists the risk factors that have been associated with scrotal SCC.

Table 2 Lowe's staging of scrotal squamous cell carcinoma

A1	Disease localized to scrotum
A2	Locally extensive disease involving adjacent structures (penis, perineum, testis or cord, and pubic bone) by continuity but without evident metastasis
B	Superficial lymph node metastasis, resectable
C	Pelvic lymph node metastasis or any unresectable metastasis
D	Distant metastasis beyond regional nodes

STAGING

In 1983, Lowe modified the initial staging system proposed by Ray and Whitmore and this staging system is still in use as outlined in Table 2[49].

The American Joint committee on Cancer (AJCC), TNM classification for scrotal SCC is similar to TNM classification for SCC in other locations (with the exception of Eyelid, Vulva and Penis) and is shown in Table 3.

For staging, clinical examination including the assessment of extension and depth of the scrotal lesion and examination of inguinal lymph nodes is mandatory. Plain chest X-ray for evaluation of the lungs is recommended. MRI scan and ultrasonography can be used for assessing the depth of the lesion and evidence of involvement of underlying structures where this is suspected. For inguinal lymph node imaging CT scan can detect enlarged inguinal and pelvic lymph nodes but is unable to identify small metastatic deposits in normal sized nodes. For nodal disease ultrasound and fine needle biopsy of suspicious lymph nodes similar to penile cancer might be of diagnostic value[50]. Similarly with improvement in sensitivity and specificity profile, 18F-FDG PET/CT might have a role in further staging of inguinal lymph nodes in patients with scrotal SCC[51]. For high-risk cases sentinel lymph node biopsy at the time of excision of primary lesion similar to penile cancer has been advocated[52].

MANAGEMENT

Few case series have been reported since 2000 (Table 4).

Primary tumour

Wide local excision of the lesion with a negative margin is the goal for the treatment of primary tumor. A surgical margin of 2-3 cm has been advocated by some authors[53], however the available guidelines for the management of cutaneous SCC recommend a 4mm radial margin for small (< 2 cm) lesions with well define edges and a radial margin of 6mm for larger lesions with poor defined edges and risk of subcutaneous extension[54]. Based on evidence from penile SCC, for < T2 disease a margin of $\geqslant$ 3 mm is considered safe where for $\geqslant$ T2 disease a surgical margin of 5-10 mm is considered appropriate[55]. Given the redundancy and laxity of scrotal skin primary scrotal closure is usually possible, but after large tumor resection primary closure might not be achievable. The defect can be reconstructed with simple closure, flap,

Table 3 TNM staging system for squamous cell carcinoma

Stage	Primary tumour	Regional lymph nodes	Distant metastasis
Stage 0	Tis = carcinoma in situ	N0 = no regional lymph node involvement	M0
Stage Ⅰ	T1 = tumour 2 cm or less	N0	M0
Stage Ⅱ	T2 = tumour > 2 cm but < 5 cm	N0	M0
	T3 = tumour > 5 cm	N0	M0
Stage Ⅲ	T4 = Invasion of deeper extradermal structures	N0	M0
	Any T	N1 = regional lymph node spread.	M0
Stage Ⅳ	Any T	Any N	M1 = distant metastasis.

Table 4 Case series with epidemiology, management and outcomes of scrotal squamous cell carcinoma published after 2000

Ref.	*n*	Design	Cohort characteristics	Summary
Stern *et al*[17], 2002	17	Prospective multi-institutional cohort study	892 men first treated with PUVA	Dose-dependent increase in the risk of genital tumors in men treated with PUVA
Seabra *et al*[19], 2007	6	Retrospective single institution	Age: 52 (31-89) Race: Ca: 2; Bl: 2; Oth: 1; Unknown: 1 Staging: LC: 4, RL: 1, DD: 1	4/6 WLE; 1/6 WLE + SLNB; 1/6 was unresectable: 1 developed LN metastasis and was treated with chemo/radiation Patient with unresectable disease and was treated with chemotherapy and subsequently died
Wright *et al*[2], 2008	151	SEER (1973-2002)	Age: 68[2] Race: Ca 117 (77.5); Bl 24 (15.9); Oth 10 (6.6)	SCC had the worse survival compared to other histological subtypes
Verhoeven *et al*[1], 2010	53	NCR (1989-2006)	Age: 56.5 Staging: Stg 0: 1 (1.9), Stg 1: 22 (41.5), Stg 2: 18 (34), Stg 3: 2 (3.8), Stg 4: 0, Unk: 10 (18.9)	SCC had the worse survival compared to other histological subtypes: 1 yr relative survival 93% 3 yr relative survival 80% 5 yr relative survival 77%
Johnson *et al*[16], 2013	269	SEER (1973-2006)	Age: 65.4[2] ± 14.9 Race: Ca 206 (76.6%), Bl 43 (16.0%), As 12 (4.5%), Hi 18 (6.7%), Oth 8 (3.0%) Staging: LC 205 (76.2%), RL 54 (20.1%), DD 10 (3.7%)	The median OS for patients with SCC was 115 (95%CI: 97-133) mo
Matoso *et al*[18], 2014	29	Retrospective multi-institutional	Age: 55 (30-74) Race: Ca 19 (65.5%), Bl 10 (34.5%) Follow up: 37 mo	25/29 WLE; 1/29 WLE + LND; 3/29 imiquimod post WLE: 13 (45%) with[1] margins required re-excision1 3/29 local recurrence: 2 WLE; 1 WLE/RT 3 /29 with lymphadenopathy lost to follow-up

[1]Positive; [2]Mean. As: Asian; Bl: Black; Ca: Caucasians; DD: Distant disease; Hi: Hispanics; LC: Local disease; NCR: Netherlands Cancer Registry; OS: Overall survival; Oth: Other; PUVA: Psoralens and ultraviolet A radiation; RL: Regional lymph node; SCC: Squamous cell carcinoma; SEER: Surveillance, Epidemiology and end results; SLNB: Sentinel lymph node biopsy; Stg: Stage; WLE: Wide local excision.

split thickness skin graft, mesh grafts or mycocutaneous grafts. Hemiscrotectomy is required for more advanced disease. Contralateral testicular transposition is an option if preservation of testis is preferable[56].

For patients with significant co-morbidities in whom surgical management is not suitable less invasive treatments such as CO2 laser for invasive SCC and 5-fluorouracil, photodynamic therapy or imiquimod for SCCIS may be considered[57,58]. Imiquimod has also been used as adjuvant to surgery post-excision[18]. Superficial small SCC and SCCIS are also amenable to mohs micrographic surgery which offers full evaluation of the surgical margins at the time of surgery and skin-sparing surgery with good functional and aesthetic outcomes[59,60].

Inguinal lymph node

Morley observed early on in the 20th century that the raphe of the scrotum does not provide a physical barrier to scrotal lymphatic drainage and the scrotum has bilateral inguinal drainage[61]. This observation forms the basis for bilateral inguinal assessment when treating patients with scrotal SCC. Data from early series suggest that similar to penile cancer only half of the patients with inguinal lymphadenopathy at the time of diagnosis, harbor metastatic disease at inguinal lymph node dissection (ILND) questioning the need for routine ILND in patients with inguinal adenopathy[62]. The authors advocated a period of follow-up (2-3 mo) after excision of primary lesion and ipsilateral ilioinguinal dissection if patient developed biopsy proven evidence of metastasis, and to defer contralateral node dissection until clinical verification of metastasis is evident.

The more contemporary algorithm for treatment of inguinal lymph node in patients with scrotal SCC has many similarities to patients with penile cancer[63]. A risk based approach to minimize morbidity associated with

ILND advocates the use of inguinal sentinel lymph node biopsy[49], with subsequent complete ILND in cases where sentinel lymph node biopsy is positive[64]. Due to rarity of this condition data from large case series are lacking and the current recommendations are largely based on experts' opinions and extrapolation of data from series with penile SCCs.

Locally advanced and metastatic disease

Adjuvant chemotherapy has been utilized in advanced stage and metastatic disease. Systemic chemotherapy is also indicated for inoperable scrotal SCC. Combination chemotherapy with methotrexate, bleomycin and cisplatin has been reported in inoperable or metastatic SCC of male genital tract with response rate of 72%, however median response duration was only 6 mo and only 14% achieved complete response[65]. Bleomycin has been utilized in the neoadjuvant setting. Adjuvant radiation has been shown to not change outcomes[32].

EMERGING THERAPIES

The era of targeted molecular and immunotherapies holds promise for management of advanced squamous cell carcinoma. Cetuximab an anti-epidermal growth factor receptor (EGFR) monoclonal antibody is an approved agent for treatment of head and neck SCC[66]. Emerging therapies for head and neck SCC include EGFR tyrosine kinase inhibitors, vascular endothelial growth factor receptor (VEGFR) inhibitors, insulin-like growth factor receptor (IGF-1R) inhibitors and inhibitors of the PI3K/AKT/mTOR pathway may have a role in the treatment of patients with scrotal SCC in future[67]. Unfortunately currently data on the efficacy of such therapies for patients with scrotal SCC is lacking.

Recently Lavens *et al*[68] showed increased EGFR expression in penile SCC. Carthon *et al*[69] evaluated EGFR targeted therapy in patients with advanced penile or scrotal cancer in a retrospective case series of twenty-four patients. Only one of twenty-four patients had scrotal SCC. This patient developed metastases to right groin with disease progression despite paclitaxel, ifosfamide, and cisplatin (TIP) chemotherapy. The addition of EGFR targeted therapy lead to reduction in tumor burden and allowed resection of residual disease. He was reported to be disease free 38 mo post EGFR therapy.

Further studies need to focus on establishing EGFR status in scrotal SCC tissue before prospective evaluation of benefits of EGFR targeted therapies. Due to low incidence of scrotal SCC, multi-institutional collaboration would be a more feasible approach. Further genomic and molecular characterization of scrotal SCC would be important in identifying key pathways and developing therapeutic targets.

CONCLUSION

Scrotal SCC is a rare clinical entity that represents one of the most common forms of scrotal malignancy. Although historically considered as an occupational disease, its epidemiology has changed in recent years and iatrogenic conditions (PUVA, Immunosuppression, *etc*.) and HPV infection play a significant role as associating conditions. Surgery is the cornerstone of the treatment algorithm for scrotal SCC. Excision of the primary lesion and a risk stratified approach for staging and treatment of regional lymph nodes is advisable. For patients with high-risk disease and negative clinical lymph nodes, sentinel lymph node biopsy can mitigate the morbidities of unwarranted ILND. For locally advanced and metastatic disease palliative chemotherapy is advocated. Future endeavors with focus on targeted therapies might hold promise for management of advanced squamous cell carcinoma. Given the rarity of this condition, multi-institutional trials in conjunction with trials for the treatment of penile SCC are likely to provide us with further knowledge in this field.

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MINIREVIEWS

Olfactory dysfunction in dementia

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Core tip: Olfactory dysfunction is often present as a symptom of a neurodegenerative disease. The potential clinical value (prodromal/pre-diagnostic, diagnostic, intervention target) of olfactory dysfunction still remains to be fully established. Standardized and easy to use tools are available and can be implemented to improve the definite differential profiles, through its widespread integration in clinical practice and research.

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Abstract

The natural aging process brings about some inevitable consequences, such as olfactory dysfunction, which is also frequently linked to numerous neurodegenerative disorders. Many age-related dementia, such as Alzheimer's disease, Vascular dementia, Parkinson's disease, and Frontotemporal Dementia often display olfactory dysfunction. Despite the overwhelming evidence of above mentioned facts, the symptomatic relevance and potential clinical and pre-clinical value of olfactory dysfunction remains overlooked by many clinicians and public alike. Olfactory dysfunction has strong practical implications on daily activities and, although not as prominent as in other mammals, olfaction is still an evolutionarily relevant sense involved in human survival (*e.g.*, smelling gas; bad food). In this work, we provide a brief review of current research related to the olfactory dysfunction profiles in different types of dementia. Additionally, we present a compilation of accessible, easy to use olfaction assessment tools; and highlight future directions in terms of improving clinical diagnosis in patient care and research.

INTRODUCTION

Although olfaction is a topic of scientific interest for both public and many professionals[1], awareness concerning olfactory dysfunction, both in healthy aging and dementia, remains limited even when considering the widespread prevalence of age-related olfactory decline. For example, half of the elderly population between 65 and 80 years of age have evident olfactory dysfunction[2-4].

Moreover, olfactory dysfunction has been acknowledged as a symptom present in dementias, such as Alzheimer's disease, vascular dementia, Parkinson and Frontotemporal Dementia (FTD)[5].

Indeed, olfactory dysfunction has a considerable prevalence in dementia, with estimated numbers as high as 100% in Alzheimer's disease (AD)[6], 90% in Parkinson's disease (PD)[7]; 96% in the frontal variant of FTD[8] and 15% in Vascular dementia (VD)[6].

In the next sections we will briefly review the main types of dementia in which olfactory dysfunction is present.

RESEARCH

The present study is a selective narrative review. The selected articles consisted of literature/articles previously known by the authors, complemented with a search on PubMed/MEDLINE focusing on olfactory dysfunction with the following search terms: olfaction (and related expressions - olfactory), Alzheimer's disease, vascular dementia, Parkinson's disease, frontotemporal dementia, Lewy body dementia, and dysfunction/impairment/deficit. Relevant articles were selected through abstract inspection. Both, reviews and clinical studies were included.

OLFACTION IN HEALTHY AGING

Olfactory loss associated with normal aging

Olfactory dysfunction has a considerable prevalence with recent estimates pointing to 3.8% in adults between 21 and 84 years of age, increasing prevalence with age (from 0.6% in those < 35 years to 13.9% among those ⩾ 65 years), with higher prevalence in men[9]. Factors involved in age-related olfactory dysfunction include changes in non-olfactory elements of the nose (*e.g.*, airflow patterns and mucous composition), olfactory neuroepithelium, olfactory bulb, central brain regions involved in olfactory processing, and neurochemical changes in the brain (for a detailed review see Doty and Kamath[10]).

Measured with University of Pennsylvania Smell Identification Test UPSIT, Djordjevic[11] and Morgan[12] refer values of approximately 33-35 as a normal olfactory performance. Doty *et al*[2] also provide a prototypical progression of olfactory decline during normal aging. They report median UPSIT values of normal olfactory performance around 37, with olfactory decline starting in the 60 s, reaching around 34 in the 70 s, and 26 in the 80 s. Lower values than those of the observed normative scores would imply a loss of olfactory abilities (for further details please see Doty *et al*[2] or Doty and Kamath[10]) For a systematic review on normative and pathological values of olfactory performance in dementia please refer to Sun *et al*[13].

Besides the normal age-related olfactory decrements, sensory and central processing impairments in the components of olfaction, are observed in number of neurodegenerative conditions[14]. These impairments might influence appetite in people with dementia and lead to dietary restrictions with negative implications on nutrition and overall health[15].

It is important to note, however, that the performance in olfactory assessment tasks might also be influenced by the assessment method as well as other brain functions such as memory. For example, Larson *et al*[16] suggest that age-related difficulties in the activation of odor knowledge (*i.e.*, odor names) might contribute to the observed age differences.

OLFACTION IN DEMENTIA

Alzheimer's disease

Alzheimer's disease is characterized by neuropathological changes, such as neurofibrillary tangles, neuritic plaques and atrophy, leading to progressively marked deficits in memory (amnestic presentation) and/or other domains such as language and visuospatial capacities (non-amnestic presentations)[17]. Olfactory bulbs are considered to be involved from the early stages of the disease and related to the neuropathological changes[18-20]. Indeed, there is evidence for considerable olfactory tau pathology in post-mortem confirmed AD, with tau pathology correlating with dementia severity[21]. Moreover, similar pathologic changes have been reported in the brain and olfactory mucosa of AD patients[14].

As expected due to the aforementioned lesional pattern, olfactory dysfunction, namely odor identification, is also a widely acknowledged, feature of Alzheimer's[22] with patients showing overt deficits in odor identification[22,23].

Olfactory dysfunction may even be present during the amnestic mild cognitive impairment (MCI) stage of Alzheimer's disease, mainly as an odor discrimination and identification difficulty and less of an odor detection deficit[24]. While cognitive and sensory characteristics associated with visuospatial, language and immediate memory skills are interconnected with olfactory discrimination, olfactory identification in itself is more related to delayed memory processing[24].

Although evidence is still limited, differential profiles between AD and other dementias have been observed which are evidently due to the underlying neurological decline characteristic of each dementia type. For example, smell identification seems to be more impaired in AD than in VD[23], however Gray *et al*[25] found impairment similarities. In the same way, AD and PD patients show equivalent levels of hyposmia (assessed through odor identification)[26]. On the other hand, there is evidence of more olfactory impairment in mild Dementia with Lewy Bodies (DLB) than in MCI or AD[27].

However, whether the available olfactory screening tests are well adjusted and specifically tailored for each of these dementias is still unclear.

Vascular dementia

Vascular dementia (VD) is characterized by cognitive decline, typically in a stepwise manner, compatible with dementia related to cerebrovascular disease[28].

VD is considered the second main cause of dementia[29] and is the topic of a considerable amount of research concerning its characterization and etiopathology. Research on olfactory dysfunction in VD is comparatively scarce. However, it has been found that VD patients score below normative performance in olfactory tests[25]. Nonetheless, when comparing VD and AD, there are mixed findings with Gray *et al*[25] reporting a similar degree of olfactory impairment between AD and VD while Duff *et al*[6] state lower performance in AD patients.

Interestingly, preliminary data, on people with history of stroke, identified them having within normal or slightly below normal olfactory performance[30].

From the aforementioned data it seems plausible to

hypothesize that the presence or absence, the range/extent and type of olfactory deficit might depend on the location and extension of vascular pathology.

Parkinson disease and other synucleinopathies

Parkinson's disease belongs to a group of neurological conditions named movement disorders, which occur due to a loss of nigrostriatal dopaminergic neurons in certain circuits of the brain[31].

Diagnosis usually occurs after the fifth decade of life typically with a slow progression of disease which is based on neurological examination and the patient's clinical history[31]. Feature symptoms include tremor, trembling of hands, legs, jaw, and face; stiffness of the limbs and trunk; bradykinesia of movements; and postural instability, resulting in impaired balance and coordination. As expected, these symptoms interfere with several daily living activities[31].

Researchers have recently directed their attention towards olfactory dysfunction in PD, as it is a prominent symptom, occurring in about 80%-90% of PD patients[32]. Moreover, olfactory dysfunction is usually prodromal to motor symptoms by several years[33,34]. Olfactory dysfunction also occurs alongside non-motor symptoms, such as in autonomic[35] (cardiovascular changes) and REM-sleep Behavior Disorders[36] (RBD), both during and at the premotor phases of PD.

Therefore, authors argue that deficits in the sense of smell may be used to assess the risk of developing PD in apparent asymptomatic patients[37].

In a population-based prospective study (longitudinal Honolulu-Asia Aging Study; HAAS), authors have demonstrated that odor identification deficits may precede the development of clinical PD in men by at least 4 years[34].

The fact that olfactory deficits appear even before confirmed PD diagnosis[38], while motor signs appear afterwards and gradually worsen, might explain the lack of relationship found between olfactory deficits and PD severity or disease duration[39].

Unsurprisingly, olfactory testing is quite sensitive and specific in distinguishing PD from other movement disorders[33,37,40]. In particular, considering that hyposmia is relatively rare in atypical Parkinson syndromes or in essential tremor, olfactory dysfunction presents added value due to its discriminatory power to differentiate neurodegenerative diseases[33]. Several tests are currently being used[10,41], some of them purposely adapted and implemented for assisting in Parkinson's Disease diagnosis, presenting appropriate sensitivity and specificity indices[42].

Decreased odor identification in PD patients has been associated with older age, greater smoking habits, more coffee intake and lower performance in cognition tests[34]. Additionally, hyposmia was also found to be predictive of dementia installation in PD patients within 3 years of assessment[43]. Furthermore, patients with severe hyposmia at baseline, display more prominent cognitive decline in the follow-up assessment.

More recently, Lee *et al*[44] divided non-demented PD participants into three groups according to their performance in an olfactory test (Cross-Cultural Smell Identification; CCSI[45]): PD-H (high score), PD-M (middle score) and PD-L (low score group). They further noted that the clinical dementia rating score was lower in the PD-H patients than in the PD-M or PD-L patients[44]. Moreover, the PD-L patients performance in the verbal memory tests was noted to be worse than that of the PD-H patients[44], which is in consonance with previous findings[34,43].

In terms of the neuropathological findings in olfactory bulb, depositions of α-Syn have been found in Lewy Body Diseases[33], with additional lesions extending to the olfactory epithelium as well as to the olfactory cortex and other olfactory-related structures[33,46]. Indeed, MRI studies confirmed that PD patients present greater Gray Matter (GM) loss in brain regions subserving primary and secondary olfactory processing, namely, bilateral piriform cortex (PC) and bilateral orbitofrontal cortex (OFC), when compared to controls (*e.g.,* Lee *et al*[47]). Additionally, right PC and left OFC volumes were correlated with the performance in olfactory tests (reduced performance correlated with lower GM volumes)[47].

These results foster the hypothesis that olfactory dysfunction is related with extranigral cortical involvement, which is consistent with the fact that the olfactory function does not improve with dopaminergic treatments[41]. Hence, other neurotransmitter systems are being considered to be involved in olfactory dysfunction (*e.g.,* cholinergic[48,49]).

Importantly, differences between studies may also be explained by the tested components such as odor threshold, discrimination and identification. Each of these olfactory components can be related to atrophy in different brain structures[47] therefore possibly contributing to the diverse smell deficits.

Finally, Takeda *et al*[41] highlight some considerations: there is actually no established standard odorants for the olfactory testing; environmental conditions such as humidity may interfere in olfactory stimulation; and sniffing (the act by one inhales air to be able to smell) may be impaired in PD patients due to motor deficits[41].

Since olfactory dysfunction is an evident feature of PD, which can be detected in early stages of the disease, to improve diagnostic precision, stronger efforts should be made to include olfactory assessment in the routine neurological examinations[41].

Frontotemporal dementia

Frontotemporal dementia is a clinical syndrome associated with shrinking/degeneration of the frontal and anterior temporal lobes of the brain[50], sometimes called frontotemporal lobar degeneration[51]. FTD was formerly known as Pick's disease[50], however, currently, FTD groups several neurological designations such as Pick's disease, primary progressive aphasia and semantic dementia[50,52].

FTD accounts for up to 10% to 20% of presenile

dementia cases and its onset tends to occur between the ages of 45 and 65 years[52,53]. The main feature in FTD is a marked change in the behavior, usually characterized by either impulsive, disinhibited or apathetic behaviors; accompanied by inappropriate social interaction, lack of social skills, lack of empathy, distractibility and compulsive behavior. Regarding language disturbances, patients may present difficulties in producing or understanding speech[50,52].

Concerning other cognitive abilities, such as spatial skills and memory, they tend to remain intact. For a careful characterization of this clinical syndrome, core features and cognitive changes in FTD, refer to the works of Snowden *et al*[52] and Neary *et al*[51].

Regarding its neuropathology, FTD is mostly characterized by cortical loss of pyramidal cells, and spongiform degeneration. In fewer cases, neuron swellings or inclusions are observed, that is, accumulation of tau proteins in neurons, visible as silver-staining aggregations (Pick bodies)[50,52].

Despite being less frequent than in Parkinson's Disease, olfactory dysfunction has been reported in FTD as well[54]. Considering the neuroanatomy of the olfactory system (involving parahippocampal gyrus and entorhinal area) and the existing compromise of the temporal cortex in FTD, olfactory dysfunction should be expected as well. One of the first studies comparing several dementia types, concluded that, when compared with AD and Semantic Dementia (SD) FTD patients do present olfactory impairment but at a lesser degree[54]. Namely, FTD patients demonstrate preserved odor discrimination abilities, whereas impairment surfaced in tasks of odor naming and odor-picture matching[54]. Additionally, the authors found a correlation between odor identification performance and measures of executive functioning[54].

In the same line of findings, McLaughlin and Westervelt[55] compared groups of FTD, AD patients and controls in an odor identification test (BSIT). The authors found that the FTD performed significantly worse than the controls, but very similar to the AD group[55]. Additionally, a tendency towards correlation between FTD severity and olfactory identification ability was observed.

In another study[8] patients with the frontal variant of FTD presented olfactory recognition deficits. The authors highlight the need to assess olfactory function in FTD patients more often, since initially these patients are commonly misdiagnosed as having depressive disorder. Considering the fact that depressive patients are expected to have better olfactory function, olfactory testing could be used to distinguish depression in elderly from a FTD diagnosis[8].

When comparing variants of FTD in an odor identification test, Omar *et al*[56] did not find differences between the subgroups, even when compared in a flavor identification task. Interestingly, these authors also found that the odor identification performance paralleled the flavor identification and both performances were correlated in clinical groups[56].

CONCLUSION

General conclusions and future directions

In the present review, in hopes of providing a primer of the topic, we summarized the main findings regarding olfactory dysfunction in aging and the main types of dementia (please refer to Table 1 for a summary of main findings in different dementias).

While there is still no solid olfactory profile for each type of dementia, olfactory assessment might prove to be a valuable tool in assisting diagnosis, as a biomarker for disease progression and a surrogate marker for disease-modifying drug efficacy[33,57]. Easy to use tests/assessments (Table 2 for an exemplifying list of standardized tests) are available and can be easily implemented from a practice-research integrative perspective, leading into an improved evidence-based profiling. However, a clear definition of the evaluated component (identification, recognition, retrieval, choice) must be regarded carefully since the discrepancies in the results reported throughout this work might have the contribution of confounding variables such as memory and naming difficulties.

Regarding these procedural issues, computerized odor systems might provide a more accurate disposal of odorants and determination of potential differential olfactory thresholds in early stages of different types of dementia. Although, functional neuroimaging studies, concerning the present topic, are scarce, if implemented more often they may assist in the clarification of the existence of different *in vivo* neural signatures related to differential olfactory impairments (*e.g.,* naming identification, confrontation identification, retrieval).

In the context of neuroimaging, despite the costs associated with sophisticated olfactometer apparatus, simpler alternatives, such as odorant saturated cotton can be implemented as well (although with less reliability). Also, semi-automatic olfactometers/odor dispensers for imaging setting can be built on a rather reasonable budget[58].

Although olfactory symptoms are a feature of dementia, which is regarded as such with a relative consensus, diagnostic guidelines seldom highlight its role or presence as a supportive feature. In this regard, screening pocket olfactory tests could be recommended in healthcare and diagnostic guidelines as a supportive test for improving differential diagnosis through fast data collection and prior screening for the purposes of a more extensive olfactory assessment. Although one may argue that these tests are not exempt of costs, there are alternatives, such as the Smell Diskettes, which can be reused for several months.

The use of olfactory baseline measurements, similar to the neuropsychological baseline assessments used in some countries, should be implemented worldwide. However, as in neuropsychological assessments, baseline olfactory results are seldom available.

As noted recently, olfactory assessments could also be included in other routine sensory assessments, such as in

Table 1 Table of main findings (comparing findings in different dementias)

Type of dementia	Profile/main findings	Differences between dementias (extent/degree/severity of impairment)
Alzheimer	Odor identification deficit, is a widely acknowledged feature of Alzheimer's	Mixed findings: AD > VD[6,23]; AD = VD[25]
VD	Olfactory performance below normative scores; Unclear differential profile with other dementias	AD = PD[26]; mild DLB > MCI/AD[27] FTD < AD[54]
PD	Decreased odor identification, which may precede the development of clinical PD	FTD = AD[55] Legend: > more impaired; < less impaired; = similar
FTD	FTD patients demonstrate preserved odor discrimination abilities, Impairments in odor naming and odor-picture	

AD: Alzheimer's disease; VD: Vascular dementia; PD: Parkinson's disease; FTD: Frontotemporal dementia; DLB: Dementia with Lewy bodies; MCI: Mild cognitive impairment.

Table 2 Easy to use common olfaction tests

Test name	Internet address
Smell Identification Test (UPSIT)[1][60]	http://sensonics.com/smell-products/smell-identification-test-international-versions-available.html
Brief Smell Identification Test[1]- also known as the Cross-Cultural Smell Identification Test[61]	http://sensonics.com/smell-products/brief-smell-identification-test.html
Pocket Smell Test[62]	http://sensonics.com/smell-products/pocket-smell-test.html
Smell Diskettes[63]	http://www.smelldiskettes.com/
Screening 12 Test (Sniffin' Sticks)[64]	http://www.usneurologicals.com/index.php?app=ecom&ns=prodshow&ref=ST_SniffinSticks

[1]Test available in multiple languages.

eye or hearing tests[59]. Routine olfactory tests, assessing several olfaction components[54], could assist not only in the detection and the discovery of causes for olfactory dysfunctions, but also aid longitudinal studies aiming to understand olfaction, and more immediately in the detection of common causes of olfactory dysfunctions, such as airway disorders and viral or bacterial infections.

In order to improve and generalize these baseline assessment practices, it is important to increase awareness of its clinical and research relevance not only among the researchers, but also among the physicians and the psychologists. Concerted informative action for generating awareness among governmental and legislative health bodies should be implemented by researchers and clinicians in all the fields of olfactory dysfunction. The absence of baseline assessments will continue to minimize accuracy in studies and clinical practices, since comparisons of patient values exclusively to group results, and not to individual levels of olfactory functioning, will only yield approximate results.

In sum, we hope that the potential of utilizing the olfactory dysfunction for diagnosis and perhaps even as intervention outcome, together with an awareness of available inexpensive and easy to implement assessment tools, can lead to its wider clinical use (integrated with research efforts). The latter mentioned proposal may very well improve dementia diagnosis and allow an establishment of differential profiles. Implementation of olfactory tests in standard neuropsychological screening and diagnostic batteries, from preclinical and early stages of dementia, will clarify if olfactory dysfunction holds any potential for aiding research progress in the field of dementia[13,24].

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Promising new treatment targets in patients with fibrosing lung disorders

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Abstract

The processes of lung fibrogenesis and fibrotic healing are common to a number of conditions with different etiologies. The lungs are the only affected organ in some cases, whereas in others, several organ systems are involved. Therapeutic options can be discussed from various perspectives. In this review, we address the localization of therapeutic targets with regard to cell compartments, including secreted ligands, cell surface, plasma membrane-cytosol interplay, cytosol and nucleus. Complex approach using stem cell therapy is also discussed. As the prognosis of patients with these disorders remains grim, treatment combinations targeting different molecules within the cell should sometimes be considered. It is reasonable to assume that blocking specific pathways will more likely lead to disease stabilization, while stem cell-based treatments could potentially restore lung architecture. Gene therapy could be a candidate for preventive care in families with proven specific gene polymorphisms and documented familial lung fibrosis. Chronobiology, that takes into account effect of circadian rhythm on cell biology, has demonstrated that timed drug administration can improve treatment outcomes. However, the specific recommendations for optimal approaches are still under debate. A multifaceted approach to interstitial lung disorders, including cooperation between those doing basic research and clinical doctors as well as tailoring research and treatment strategies toward (until now) unmet medical needs, could improve our understanding of the diseases and, above all, provide benefits for our patients.

Key words: Interstitial lung disease; Treatment; Idiopathic pulmonary fibrosis; Connective tissue disease; Cell compartments; Signaling molecules; Signal transducers; Transcription factors

Core tip: Novel treatment targets in patients with fibrosing interstitial lung diseases are summarized. Targets are listed according to defined cell compartments. Ongoing clinical studies focusing on some of the promising targets provide insight into current progress in lung fibrosis research.

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INTRODUCTION

The processes of lung fibrogenesis and fibrotic healing are common to a number of conditions with different etiologies. The lungs are the only affected organ in some cases, whereas in others, several organ systems are involved. There are several similar features that can be observed in adult patients with fibrosing lung disorders: *e.g.*, a history of exposure to inhaled antigens (organic or

Table 1 Interstitial lung diseases with a fibro-proliferative pattern, radiologic/histologic phenotypes and new treatment modalities

Etiology	Radiologic/histopathologic phenotype	New treatment modalities studied
Lung-specific involvement		
Inhalation of organic antigens (*e.g.*, EAA)	NSIP, UIP, OP, DIP, AIP	No
Inhalation of inorganic materials (*e.g.*, asbestosis)	NSIP, UIP, OP, DIP, AIP	No
Drug and radiation toxicity	NSIP, UIP, OP, DIP, AIP	No
Idiopathic pulmonary fibrosis	UIP ± NSIP	Yes
Idiopathic nonspecific interstitial pneumonia	NSIP ± UIP	No
Systemic involvement		
ILDs associated with connective tissue diseases	NSIP, UIP, OP, DIP, AIP	Yes
Sarcoidosis and other granulomatoses	NSIP, UIP, OP, DIP, AIP	Yes

EAA: Extrinsic allergic alveolitis; IPF: Idiopathic pulmonary fibrosis; NSIP: Nonspecific interstitial pneumonia; ILD: Interstitial lung disease; UIP: Usual interstitial pneumonia; OP: Organizing pneumonia; DIP: Desquamative interstitial pneumonia; AIP: Acute interstitial pneumonia.

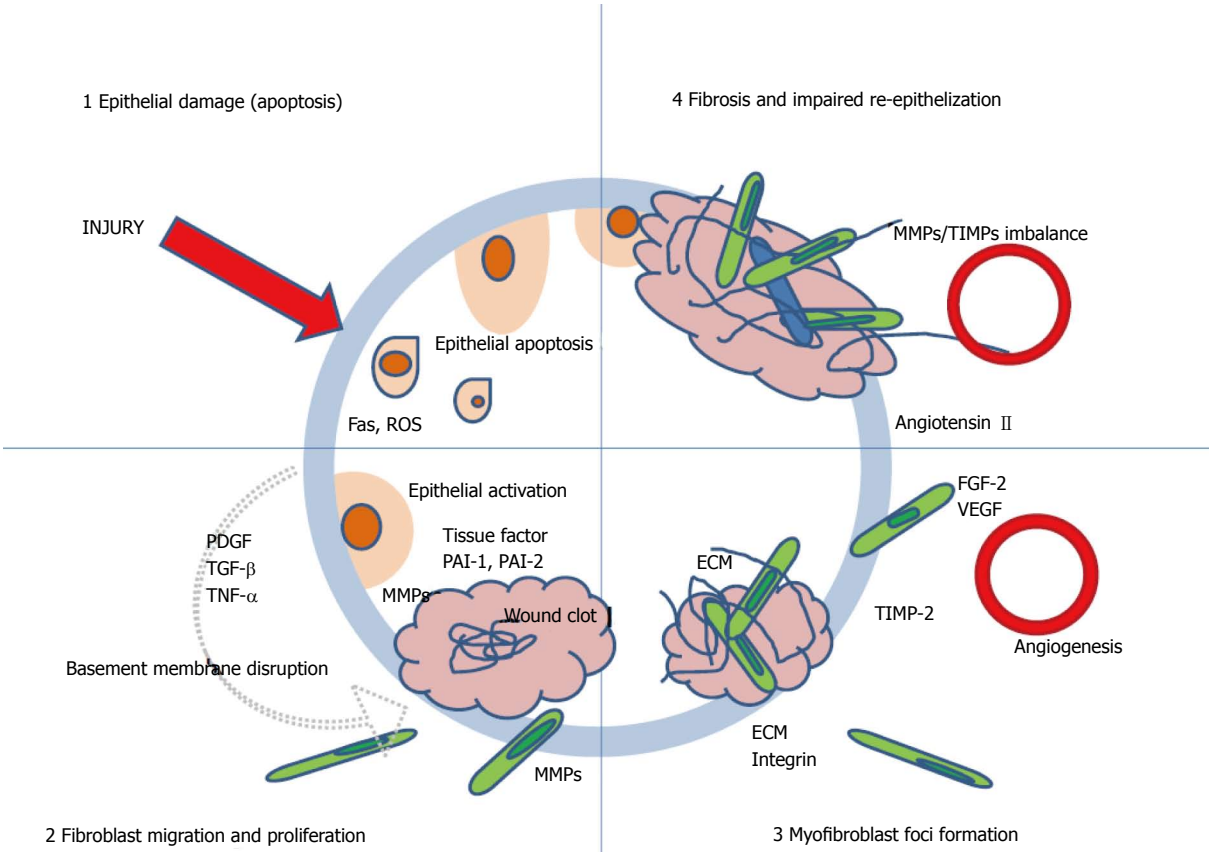

Figure 1 Suggested pathogenesis of idiopathic pulmonary fibrosis. ROS: Reactive oxygen species; PDGF: Platelet-derived growth factor; TGF-β: Transforming growth factor beta; TNF-α: Tumor necrosis factor alpha; MMPs: Matrix metalloproteases; PAI: Platelet activator inhibitor; ECM: Extracellular matrix; TIMP: Tissue inhibitor of metalloproteases; FGF: Fibroblast growth factor; VEGF: Vascular endothelial growth factor.

inorganic compounds, smoking), respiratory infections (viral), extra-esophageal reflux, impaired coagulation cascade, signs of immune system disorders with detectable autoantibodies, and genetic susceptibility[1-5]. In some patients, both fibrosis and inflammation may be observed; in contrast, in the pathogenesis of idiopathic pulmonary fibrosis (IPF), inflammation plays a relatively minor role[6].

The spectrum of interstitial lung diseases with a fibro-proliferative pattern of healing is summarized in Table 1.

Until recently, most treatment options in patients with interstitial lung disorders have focused on inflammation and lung fibrosis, relying on anti-inflammatory and immunosuppressive agents[7]. However, these strategies have been found to be effective only in specific groups of patients (patients with connective tissue-associated ILD, history of inhalation of organic antigens, drug- and radiation-induced ILD, sarcoidosis or other granulomatoses). In IPF patients, as documented in the Panther study, these treatments not only failed, but they seemed to negatively impact the mortality and morbidity outcomes of patients[8].

Figure 1 depicts the hypothesized mechanism underlying the pathogenesis of IPF. Repeated micro-injuries to

Table 2 Potential treatment targets in patients with fibrosing lung disease, according to target location

Target	Potential molecular target
Signals from other cells	Cytokines, survival factors, chemokines, hormones, transmitters, growth factors, extracellular
Autocrine signals	matrix compounds, Wnt, Hedgehog, death factor
Cell surface	Cytokine receptors, receptor tyrosine kinase, G protein-coupled receptors, integrins, Frizzled, Patched, Fas receptor, ion channels
Plasma membrane-cytosol interface	Kinases
	miRNAs
Cytosol signal transducers	Apoptosis-related proteins
Nucleus	Transcription factors
	Epigenetic modifiers

miRNA: Micro-ribonucleic acid.

Table 3 Ongoing clinical studies in idiopathic pulmonary fibrosis patients

Target	Potential molecular target	Ongoing clinical study
Signals from other cells	Interleukin 13	Lebrikizumab NCT01872689
Autocrine signals	Connective tissue growth factor	Tralokinumab NCT02036580
		FG-3019 NCT01890265
Cell surface	Lysophosphatidic acid receptor	Lysophosphatic acid receptor antagonist-NCT01766817
	Lysyl oxidase LOXL2	Simtuzumab NCT01769196
	CD20	Rituximab NCT01969409
	Androgen receptor	Nandrolone decanoate NCT02055456
Plasma membrane-cytosol interface	Phosphoinositol kinase PI3K	Phosphoinositol kinase PI3K inhibitor NCT01725139
Cytosol signal transducers	Avβ6 integrin	STX-100 NCT01371305
Nucleus		None
Stem cells		Autologous adipose-derived adult stem cells NCT02135380
		Autologous mesenchymal bone marrow-derived stem cells NCT01919827
		Allogenic human mesenchymal stem cells NCT02013700

the alveolar epithelium seem to play a key role in the initiation of the disease. Fibroblasts are attracted to the site of injury, proliferate and eventually form fibroblast foci with exaggerated extracellular matrix production[9]. Some of the epithelial type II alveolar cells may undergo transdifferentiation into fibroblasts and become activated[10]. Developmentally active programs, including Sonic hedgehog (Shh), Notch and Wingless-related MMTV integration site (Wnt), were found to be repeated in IPF[11,12]. However, unlike in "normal" development, these pathways seem to be dysregulated, resulting in an overactive development phenotype[13].

These clinical observations as well as new insights into the pathogenesis of fibrosing lung diseases have led to a vigorous search for alternative treatments. Potential targets for the treatment of fibrosing ILD are listed in Table 2. Table 3 presents ongoing clinical studies in IPF patients.

SECRETED LIGANDS (SIGNALS FROM OTHER CELLS, AUTOCRINE SIGNALS)

Cytokines, chemokines, growth factors and their receptors have been widely investigated in patients with various fibrosing lung diseases. These molecules play a role in inflammation, fibrogenesis and angiogenesis, and most of them have been found to be somehow involved in the pathogenesis of fibrosing lung disorders[14]. Although *in vitro* studies and experiments using mouse models have provided promising results suggesting that blocking certain chemokines or cytokines could prevent the progression of lung fibrosis, results from clinical studies have not been convincing. For instance, although tumor necrosis factor alpha (TNF-alpha) inhibitors were found to be useful in the management of connective tissue diseases (CTDs) and sarcoidosis, they were demonstrated to have no benefit in patients with marked lung fibroproliferation, such as in IPF patients[15,16]. Moreover, in patients with pulmonary involvement due to CTDs, the role of TNF-alpha inhibitors has yet to be established[17]. Other agents, such as interleukin-13 (IL-13) inhibitors, chemokine (C-C motif) ligand 2 inhibitors, connective tissue growth factor (CTGF) inhibitors, transforming growth factor (TGF) inhibitors and (beta 1 isoform) lysyl oxidase-like (LOXL) 2 inhibitors, are currently the subject of clinical studies[18]. TGF beta is considered an important mediator of fibrotic processes. It plays a role in in wound healing, extracellular matrix production and angiogenesis. However, it is also involved in inflammatory responses and can exhibit both pro-inflammatory and anti-inflammatory properties. TGF beta also plays an ambiguous role in oncogenesis: it can inhibit the growth of some tumor cells while enhancing migration and growth in others[19]. As the fibrogenic properties of TGF beta

have been known and extensively studied, an anti-TGF beta antibody (fresolimumab) has already been tested in IPF patients. Current strategies are directed mostly at downstream mediators, which are thought to have fewer harmful effects on tissue homeostasis[20].

Oxidative stress is considered to be a key mediator in IPF pathogenesis. It is not known whether this is due to the overproduction of reactive oxygen species (ROS) or to the diminished scavenger capacity of various cells[21]. NADPH oxidase (NOX) is one of the ROS-generating enzyme systems expressed by alveolar epithelial cells, endothelial cells, macrophages, neutrophils, mesenchymal cells and smooth muscle cells. Several isoforms of NOX have been characterized, with NOX-1, NOX-2 and NOX-4 appearing to be the most relevant in IPF pathogenesis. Specific NOX inhibitors may prove to be effective drug targets in IPF[22].

CELL SURFACE

Pirfenidone was found to inhibit the synthesis of TGF beta and TNF alpha, even though the underlying mechanism has yet to be elucidated. Compared to placebo, pirfenidone delays the progression of IPF and mortality, and it is currently the only registered molecule for IPF treatment in some countries[23].

Lung fibrosis with distortion of vessel architecture is accompanied by enhanced coagulation. The primary function of the coagulation cascade is to promote hemostasis and limit blood loss in response to tissue injury. However, coagulation also plays a pivotal role in inflammatory and tissue repair responses, including lung fibrosis[24]. Hyperplastic alveolar epithelium in patients with fibro-proliferative lung disorders might be an important source of several coagulation-promoting factors. There have been several studies on the potential therapeutic role of warfarin, but these resulted in a strong recommendation against the use of warfarin in IPF treatment. Further studies have shown that other components of the coagulation cascade can be targeted. Proteinase-activated receptor 1 (PAR-1) is a major high-affinity receptor for thrombin and its activation leads to a number of pro-fibrotic events, including the proliferation of fibroblasts and their differentiation into myofibroblasts[25]. PAR-1 has been suggested as a major player in endothelial-epithelial barrier disruption. Atopaxar and vorapaxar inhibit PAR-1 and may represent possible options in IPF treatment[26].

Given that fibroblast proliferation and extracellular matrix production are the hallmark of fibrotic lung diseases, huge efforts have been made to investigate fibroblast biology and signaling[27]. Lung fibroblasts derived from IPF patients have enhanced motility compared to their normal counterparts. This hypermotile phenotype of fibroblasts is thought to be driven by ligation of urokinase with its receptor (uPAR), which leads to the formation of unique lipid raft platforms. Blocking fibroblast migration *via* uPAR represents one possible future treatment option for IPF patients[28].

Another therapeutic approach may involve blocking signaling mechanisms in cells that are common to multiple pathways. The pro-fibrotic effect of TGF beta 1 and basic fibroblast growth factor (FGF) was found to be dependent on a Ca^{2+}-activated K^+ channel ($K_{Ca}3.1$). Inhibiting this channel can block the function of pro-fibrotic human lung myofibroblasts. This makes the $K_{Ca}3.1$ channel an attractive pharmacological target, particularly as it appears to play only a minor role in normal physiology[29]. So far, inhibitors of this channel have been used in humans with sickle cell disease with few side effects.

PLASMA MEMBRANE-CYTOSOL INTERPLAY

Tyrosine kinase (TK) inhibition also attenuates downstream signaling in cells and might be useful if a mutation in the gene coding for tyrosine kinase leads to uncontrolled activation of the cell, manifested as unregulated cell cycle or protein production. Several authors have suggested that similar features and pathogenic pathways might play a key role in idiopathic pulmonary fibrosis and lung cancer[30]. In both diseases, epigenetic and genetic changes result in altered responses to regulatory signals, abnormal expression of microRNAs and activation of specific signaling pathways, which raises suspicion that a similar treatment approach could be useful. Inhibitors of TKs or TK-dependent signal transduction pathways might be very helpful in controlling the growth of cancer cells[31]. Although studies with imatinib mesylate in IPF patients showed a lack of efficacy, this compound is not the only inhibitor of TK signal transduction that has been tested. Nintedanib is a triple inhibitor of TK receptors (platelet-derived growth factor, vascular endothelial growth factor, and fibroblast growth factor receptors) and is just one of the new drugs that may improve the prognosis of IPF patients[32]. Recently published data show that nintedanib reduces lung function decline and slows the progression of IPF[33].

Another member of the protein kinase family is a group of serine-threonine kinases. Rho-kinase (ROCK) is a member of this group and is involved in the regulation of cell movement and shape and plays a role in the function of the tumor suppressor gene PTEN and the mechanism of apoptosis[34]. The rho-kinase inhibitor fasudil has potential as a new treatment in systemic scleroderma patients. Additionally, this molecule was found to inhibit lung fibrosis in the bleomycin mouse model and has been suggested as a possible treatment for IPF patients[35].

As mentioned above, pathological remodeling of the extracellular matrix by fibroblasts plays a role in IPF pathogenesis. Parker *et al*[36] noted that expansion of fibrotic lesions after the initial insult leading to fibrogenesis is likely driven by a positive feedback loop between fibroblasts and the extracellular matrix. An interesting option for blocking this loop could be miR-29, which is a potent negative regulator of extracellular matrix genes. Gener-

ally, miRNAs are a type of non-coding, small-sized, evolutionarily preserved RNA and they act as repressors of gene expression at the post-transcriptional level. Other miRNAs that may play a role in IPF and may represent treatment opportunities include miR-21, miR-155 and miR-200[37].

NUCLEUS

Novel treatment targets are not just limited to the cell surface or cytoplasm; some potential treatments also target the nucleus. Transcription factors are proteins necessary for the transcription of DNA into mRNA. There are specific transcription factors involved in development, response to environmental stimuli, cell cycle control and response to intercellular signals. Immediate-early response transcription factor (Egr-1) takes part in mitogenesis and differentiation. It is thought to be a tumor suppressor gene. Egr-1 has been found to play a role in the fibrotic process, in addition to oncogenesis. It can regulate the expression of extracellular matrix components, matrix remodeling enzymes and fibrogenic cytokines, and drive myofibroblast differentiation[38,39]. Although several drugs have been found to have potent inhibitory activity against Egr-1 induction or activity (*e.g.*, mycophenolate mofetil, cyclosporine, imatinib mesylate), clinical studies have only supported their potential use in a subset of patients (ILD associated with CTD)[40]. Although mycophenolate mofetil, cyclosporine or imatinib mesylate may be useful in patients with autoimmune disorders that also affect the lung, they are not routinely recommended for IPF patients. The role of simvastatin and rosiglitazone still needs to be established[41,42].

Gene therapy has been suggested as a potential treatment option in numerous respiratory diseases. Gene preparations can be administered to target organs by intravenous, intramuscular or intra-tumor injections. One possible noninvasive delivery strategy includes intranasal administration[43]. Effective introduction to the lungs is thought to be possible because of the large absorption area of the mucous membrane and high perfusion. Most research in this area is concentrated on monogenic diseases and lung cancer, with few data on IPF thus far. Gene therapy has been combined with conventional treatment in cancer models and seems to offer interesting treatment possibilities in cases with a known genetic cause - especially for familial lung fibrosis due to short telomere syndrome or MUC5B (gene for mucin) gene polymorphisms[44-46].

TISSUE REPAIR- POTENTIAL FOR STEM CELLS

Stem cells represent a more complex treatment approach than specific molecular targeted therapy. Stem cells were expected to be the ultimate strategy for restoring diseased lungs, including structural repair (engraftment of cells) and immunomodulation. Endogenous lung progenitors, endothelial stem cells, induced pluripotent cells, mesenchymal stem cells and epithelial stem cells have all been proposed as prospective treatments, especially for IPF patients[47,48]. Intravenous and intratracheal administration of epithelial type Ⅱ alveolar cells is now being tested in humans. Mesenchymal stem cells (MSCs) were found to be immunosuppressive, they have low immunogenicity and they home to sites of injury after systemic administration. However, MSCs appear to be more efficient in resolving diseases with high inflammatory activity and are less able to preserve organ function or restore cell derangements in patients with chronic disease. It has been suggested that systematically administered bone marrow MSCs can differentiate into type Ⅱ epithelial cells and suppress the expression of proinflammatory and profibrotic genes[49,50]. However, ongoing studies in IPF patients were designed as safety studies and their results are still somewhat controversial. The therapeutic potential of bone marrow MSCs may be further enhanced by using a cell-based gene delivery approach.

CHRONOBIOLOGY

Although circadian rhythms have proved to be strong regulators of many tissue-specific genes, the data concerning lung fibrosis patients are limited. A study by Pekovic-Vaughan suggests that susceptibility to oxidative stress lung injury may vary during the day, because the activity of redox-sensitive transcription factor Nrf2 correlates with the circadian rhythm[51]. Not only does Nrf2 enhance oxidative stress, it also points toward a new site for lung fibrosis research[52]. Chronobiology has demonstrated that timed drug administration can improve treatment outcomes.

NON-IPF DISORDERS

In patients with non-IPF fibrosing interstitial lung disorders that continue to progress despite conventional immunosuppression, the anti-CD20 monoclonal antibody rituximab has been tested and appears to be an effective therapeutic intervention, regardless of the final diagnosis[53]. However, the data on the optimal treatment strategy in CTD-related fibrosing lung disease are still limited. In patients with systemic lupus erythematosus (SLE), belimumab (IgG1 lambda monoclonal antibody binding circulating B-lymphocyte stimulator) may be an attractive alternative to rituximab. The anti-interferon antibody sifalimumab is being studied in SLE patients and may represent a new treatment option for other autoimmune disorders[54]. Whether it could also be beneficial in patients with associated interstitial lung disease is still unknown.

Pulmonary involvement in systemic sclerosis (SSc) patients is common and it is considered to a major cause of death in SSc patients. The pathogenesis of SSc is characterized by significant accumulation of inflammatory cells in the lung parenchyma, even in patients with an otherwise usual interstitial pneumonia (UIP) pattern

of interstitial lung fibrosis. There is an ongoing debate regarding the optimal immunosuppressive agents for SSc ILD patients, especially concerning newer agents such as mycophenolate or rituximab. According to some authors, cyclophosphamide should not be routinely replaced by mycophenolate in SSc ILD subjects[55]. Several studies have indicated that rituximab can be useful, but it should be further investigated[56]. Pirfenidone, STX-100 and fasudil represent interesting possible treatment options in SSc ILD patients.

CONCLUSION

Despite recent advances and deeper insight into the pathogenesis of fibrosing lung disorders, we are still unable to successfully treat our patients. Several points need to be addressed, and several intriguing questions need to be answered: (1) How do we define effective treatment? Should effective treatment be defined in terms of disease stabilization and prevention of further decline in lung function? Should we define effective treatment as an improvement in patient quality of life, without necessarily extending it? Should the optimal definition of "effective treatment" include restoration of the lung parenchyma and resolution of both fibrosis and inflammation (if any is present)? It is reasonable to assume that blocking specific pathways will more likely lead to disease stabilization, while stem cell-based treatments could potentially restore lung architecture. Gene therapy could be a candidate for preventive care in families with proven specific gene polymorphisms and documented familial lung fibrosis; (2) Radiological and histopathological patterns of usual interstitial pneumonia (UIP) may be observed in patients with fibrosing lung disease of known cause, such as CTDs, drug-induced lung fibrosis or in patients with a history of exposure to inorganic/organic inhalation antigens. Can any of the above-mentioned therapeutic approaches also be used in non-IPF patients with a radiographic/histopathologic UIP pattern? (3) Should a combination of drugs and therapeutic approaches be used instead of monotherapy? and (4) Similarities between IPF and lung cancer were listed above. What should we learn from the oncological approach? Should we use different treatment strategies according to the stage of the disease and the individual genetic background of patients? If so, what should the staging of lung fibrosis be based on?

We believe that a multifaceted approach to IPF, including cooperation between those doing basic research and clinical doctors as well as tailoring research and treatment strategies toward (until now) unmet medical needs, could improve our understanding of the disease and, above all, provide benefits for our patients.

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Recurrent anterior shoulder instability: Review of the literature and current concepts

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Abstract

The purpose of this review article is to discuss the clinical spectrum of recurrent traumatic anterior shoulder instability with the current concepts and controversies at the scientific level. Because of increasing participation of people from any age group of the population in sports activities, health care professionals dealing with the care of trauma patients must have a thorough understanding of the anatomy, patho-physiology, risk factors, and management of anterior shoulder instability. The risk factors for recurrent shoulder dislocation are young age, participation in high demand contact sports activities, presence of Hill-Sachs or osseous Bankart lesion, previous history of ipsilateral traumatic dislocation, ipsilateral rotator cuff or deltoid muscle insufficiency, and underlying ligamentous laxity. Achieving the best result for any particular patient depends on the procedure that allows observation of the joint surfaces, provides the anatomical repair, maintains range of motion, and also can be applied with low rates of complications and recurrence. Although various surgical techniques have been described, a consensus does not exist and thus, orthopedic surgeons should follow and try to improve the current evidence-based treatment modalities for the patients.

Key words: Recurrent instability; Glenohumeral joint; Dislocation; Shoulder; Review

Core tip: Recurrent anterior instability of the shoulder is a complex disorder which mainly affects younger population, and generally requires surgical intervention to restore joint stability. Although many authors published good to excellent clinical results regarding various techniques described in the literature, a consensus on the ideal treatment modality has not been established yet. In this review article, we present an overview of recurrent anterior instability of the glenohumeral joint and discuss the treatment options with current concepts.

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INTRODUCTION

Anterior glenohumeral dislocation during sports activities or social life is one of the most commonly seen pathologies in the clinical practice of orthopedic traumatology. The prevalence of anterior glenohumeral instability has been reported as 2%[1]. The glenohumeral joint has been

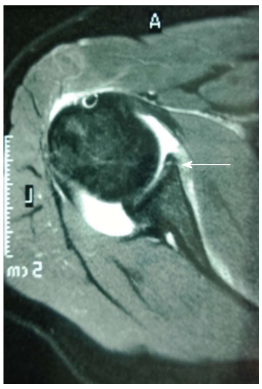

Figure 1 The Bankart lesion on magnetic resonance imaging.

reported as the most commonly dislocated synovial joint of the human body[2]. Forced abduction and external rotation of the shoulder can cause anterior dislocation resulting in instability[3]. Participation in athletics can place exceptional demands on the musculoskeletal system, especially the shoulders of the ones who perform overhead activities[4]. Shoulder instability most commonly affects people who are in their late teens to mid-thirties[5]. A major problem following a primary traumatic anterior shoulder dislocation is the high risk of recurrence among young patients[6]. Rhee *et al*[7] mentioned that these injuries occur at a younger age, with higher rates of recurrence, and with shorter intervals between initial injury and recurrent instability events among athletes. Because of increasing participation of people from any age group of the population in sports activities, health care professionals dealing with the care of trauma patients must have a thorough understanding of the anatomy, patho-physiology, risk factors, and management of anterior shoulder instability. Degenerative arthropathy in the shoulder joint is generally the final result of chronic instability[8]. The purpose of this review article is to discuss the clinical spectrum of recurrent traumatic anterior shoulder instability with the current concepts and controversies at the scientific level.

FUNCTIONAL ANATOMY

Shoulder joint is a complex anatomical and biomechanical structure which functions in a manner that several stabilizers play role in a special harmony in different stages of motion. Stability of the shoulder is established by the glenohumeral articulation, labrum, glenohumeral ligaments, rotator cuff, and deltoid muscle. The contact surface of the humeral head with the glenoid is about 30%, which means that the joint has a limited osseous constraint so that the primary stability is due to other soft tissue components rather than the osseous contact[9]. This allows a very large range of motion but in turn, a predisposition to subluxation or dislocation as well. The anterior labrum plays a key role in anteroposterior stability as it deepens the glenoid cavity up to 50%[10]. Therefore, injuries causing detachment of the labrum from its original anatomic location can cause recurrent anterior instability. A Bankart lesion, which is defined as the anteroinferior detachment of the glenoid labrum, was demonstrated in 87% to 100% of first-time dislocations[11-13] (Figure 1).

The superior, middle and inferior glenohumeral ligaments unite to form a soft tissue complex which functions as a static stabilizer for the joint. Each component of this ligamentous structure has its unique contribution to joint stability during different stages of motion. The coracohumeral ligament also functions synergistically with the superior glenohumeral ligament in resisting inferior translation of an adducted shoulder joint[14]. The middle and inferior glenohumeral ligaments provide anterior stability in different degrees of shoulder abduction and external rotation. The anteroinferior portion is the weakest part of the glenohumeral ligament complex in an abducted and externally rotated shoulder.

The deltoid muscle and the rotator cuff are named as the primary dynamic stabilizers which are active during shoulder motion in all axes[9]. The pathologies affecting the deltoid muscle and the rotator cuff not only cause decrease in range of motion of the shoulder joint but also disturbance of the biomechanical stability. Muscle weakness and/or imbalance of the dynamic stabilizers have been reported as leading to recurrent anterior shoulder instability[15-20].

CLINICAL EVALUATION

A detailed history and a careful physical examination of the patient are the primary steps of the clinical assessment. Mechanism of the first incident, time period from the first dislocation to recurrent instability, activities leading to recurrence or apprehension, number of dislocations, and history of reducibility without emergency visit should be noted for each patient. Schrumpf *et al*[14] mentioned the importance of distinguishing traumatic subluxation or dislocation and multidirectional instability, as the pathophysiologies and the treatment approaches of them were far different.

Physical examination is crucial in understanding the mechanism of recurrent dislocations. Comparative evaluation of both shoulders should be performed. Any visible deformity and/or muscle atrophy with respect to contralateral shoulder, or any scar tissue related to past trauma or surgery are important and simply recognizable just by a careful inspection. Active and passive range of motion in all planes should be measured and noted for both shoulders in every patient. Generalized ligamentous laxity should be kept in mind and checked in every patient. Axillary nerve examination should always be considered as critically important during clinical assessment. Apprehension and relocation tests as provocative examination are the fundamentals of clinical evaluation of any patient with a medical history of recurrent instability (Figure 2). Anterior apprehension test is performed with the shoulder in 90 degrees of abduction and the elbow in 90 degrees of flexion, with forced external rota-

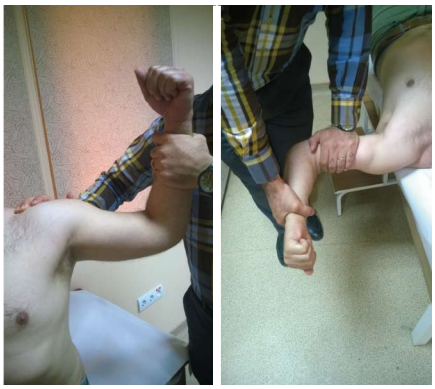

Figure 2 Apprehension and relocation tests.

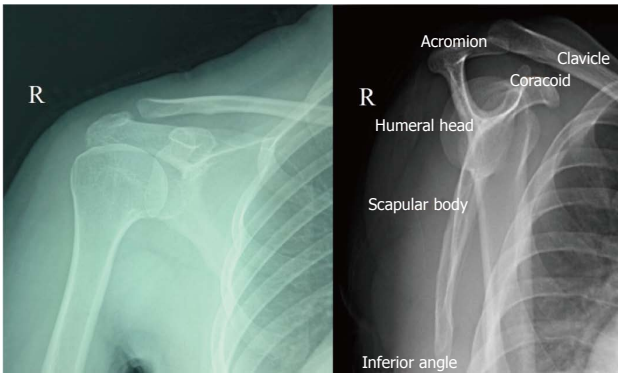

Figure 3 Anteroposterior shoulder view and scapular Y view radiographs.

tion applied to the extremity as anterior stress is applied to the humerus. Relocation test is performed while the patient is supine and the shoulder in 90 degrees of abduction and external rotation. Anterior stress is applied to the humerus in various degrees of abduction. When the pain or apprehension occurs, posterior-directed force is applied to relocate the humeral head. If the release of posteriorly directed stress used to relocate the humeral head produces a feeling of apprehension or subluxation, it indicates anterior instability. Laxity specific to lesions of inferior glenohumeral ligament can be distinguished by performing the hyperabduction test (Gagey's sign)[21].

Anteroposterior, axillary lateral and scapular Y-view images are the primary routine radiographic evaluation tools in patients with recurrent instability (Figure 3). Different specific radiographic imaging techniques including apical oblique view, West point axillary view or Stryker notch view can also be valuable to detect particular pathologies related to patient's complaint. West point axillary view is used to evaluate for a glenoid rim fracture, whereas Stryker notch view is for Hill-Sachs lesion. However, a three-dimensional computed tomography is gold-standard technique to detect osseous pathologies as well as quantifying the degree of bone loss[22]. Magnetic resonance imaging (MRI) is a very useful tool in detecting soft tissue pathologies. Gadolinium-enhanced MRI is a minimally invasive and effective radiographic method to diagnose any capsular or labral damage pre-operatively.

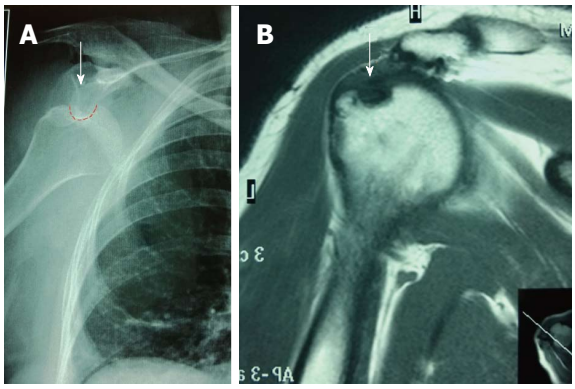

Figure 4 Engaging Hill-Sachs lesion leading to recurrent anterior instability (A) and Hill-Sachs lesion on magnetic resonance imaging (B).

RISK FACTORS FOR RECURRENT INSTABILITY

Many different risk factors for recurrent anterior shoulder dislocation such as young age, participation in high demand contact sports activities, previous history of ipsilateral traumatic dislocation, presence of Hill-Sachs or osseous Bankart lesion, ipsilateral rotator cuff or deltoid muscle insufficiency, and underlying ligamentous laxity have been described[1,23-30]. Ramsey *et al*[31] reported that traumatic anterior instability of the shoulder is associated with a high rate of recurrence in young patients. Marans *et al*[32] reported 100% redislocation rate in twenty-one skeletally immature patients who were treated with a sling.

According to Porcellini *et al*[33], age at the time of the first dislocation, male sex, and the time from the first dislocation until surgery were significant risk factors for recurrence. However, in a prospective multicenter clinical study with twenty-five years of follow-up no significant differences with respect to gender could be demonstrated[34]. According to the results of a Level-I prospective cohort study subjects with a prior history of glenohumeral joint instability were approximately five times more likely to experience a subsequent instability event, regardless of direction[35]. Although glenoid bone loss is more common, engaging Hill-Sachs lesions can also be a cause of recurrent instability[36] (Figure 4). A Hill-Sachs lesion, which is defined as an osseous defect resulting from forceful impaction on the posterolateral side of the humeral head during anterior dislocation, was demonstrated as high as 90% to 100% of the patients with shoulder instability[11-13]. Hovelius *et al*[34] reported that immobilization was not found to be associated with the risk of redislocation.

TREATMENT

Recurrent anterior shoulder instability resulted from an initial traumatic dislocation can be as serious as preventing an athlete from returning to sports. Without proper treatment, chronic instability generally results in a degen-

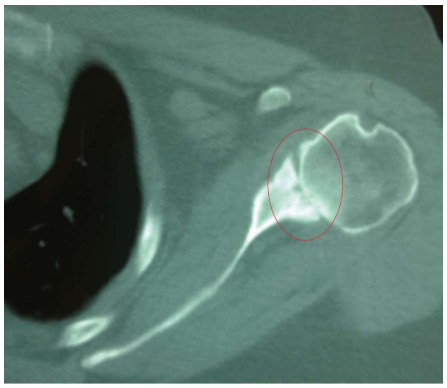

Figure 5 Degenerative arthritis secondary to chronic instability.

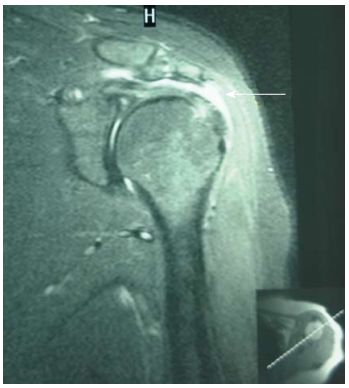

Figure 6 Rotator-cuff tear in a patient with recurrent anterior instability.

erative arthropathy in the shoulder joint (Figure 5). The common surgical interventions address the labral tears as well as the capsular laxity which are generally the basic underlying pathologies. Surgical repair of any accompanying rotator cuff tear should also be included in the treatment process (Figure 6). Although many different surgical techniques have been described to treat traumatic recurrent anterior instability of the shoulder, the best method still remains controversial. A successful clinical outcome basically requires an accurate surgical technique applied *via* adequate exposure. The main objective of the treatment should be considered as the most anatomical repair of the well defined pathological condition leading to recurrent instability. Achieving the best result for any particular patient depends on the procedure which allows observation of the joint surfaces, provides the anatomical repair, maintains range of motion, and also can be applied with low rates of complications and recurrence.

Open and arthroscopic procedures are treatment options in patients with traumatic recurrent anterior instability of the shoulder which is unresponsive to conservative measures. The arthroscopic treatment of glenohumeral instability requires that a level of expertise be achieved and retained[31]. Although open stabilization was reported as more effective than arthroscopic stabilization in the aspect of post-operative recurrence rates in 1990s, clinical outcomes have become similar in time. Technological improvements in arthroscopic instrumentation as well as the development of the innovative surgical techniques as a result of the cumulative experience with improved understanding of the factors leading failure in such patients have played the key role[24,33,37-43]. In their prospective randomized study, Fabbriciani *et al*[41] reported equal results between arthroscopic and open surgical repair of Bankart lesion in the aspect of recurrence. According to the results of another recent prospective randomized clinical trial comparing open and arthroscopic techniques, the difference in quality of life between the patients in the two groups was neither significant nor clinically important at two years follow-up; however significantly lower risk of recurrence was obtained in patients for whom open repair was preferred[5]. Surgical treatment of athletes participating in contact sports is still controversial. Rhee *et al*[44] compared the results of arthroscopic and open stabilization in young contact athletes and reported recurrent instability as 25% in the arthroscopic group and 13% in the open stabilization group. Some authors mentioned that athletic activity plays a greater role in post-operative recurrence than the surgical method used for stabilization[39,45].

Bone loss either on the glenoid or the humeral head may cause or complicate recurrent shoulder dislocations. Recurrent episodes of anterior instability of the shoulder joint may cause Hill-Sachs or osseous Bankart lesion get larger which leads further instability[46,47]. Therefore, isolated Bankart repair is generally not sufficient as the surgical management of the patients with osseous lesions. In their study which evaluates the morphology of the glenoid cavity in patients with recurrent anterior instability of the shoulder, Sugaya *et al*[48] concluded that 10% of subjects did not have osseous pathology, 40% had bony erosion, and 50% had an osseous Bankart lesion. If bone loss is greater than 25% of the glenoid surface, surgical treatment should include a bony reconstruction procedure[49]. Ideal technique for the surgical management of bony defects on the glenoid rim is controversial. Reduction and fixation of the displaced glenoid rim fracture, transfer of the coracoid process to the anterior glenoid, and reconstruction by using autograft or allograft bone block are the methods to restore the normal width and depth of the glenoid cavity. Basically, all of the various surgical interventions aim to restore more anatomic glenoid morphology to prevent recurrent instability. Park *et al*[50] reported that following successful fixation of the glenoid fracture in its anatomic position, fragments unite and survive without resorption at one year. When the bone loss is greater than 25% of the glenoid surface with a missing fragment, transfer of the coracoid process to the anterior glenoid rim as a structural block is the best approach. Bristow, Latarjet, or Trillat procedures are effective, most widely known and used techniques of coracoid transfer into the glenoid lesion. Latarjet procedure, which was first described in 1954, is the transfer of the coracoid process through the subscapularis tendon to provide an osseous block during joint motion. Bristow procedure is the technique in which the terminal 1 cm

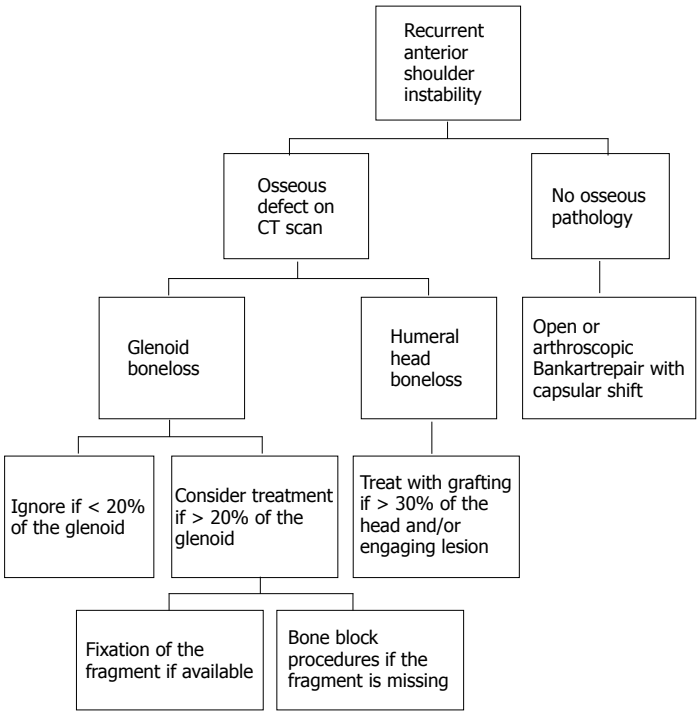

Figure 7 Treatment algorithm that we follow in our clinical practice.

of the coracoid is transferred together with the conjoint tendon onto the neck of the scapula through a horizontal slit in the subscapularis muscle. In Trillat procedure, the coracoid is osteotomized following an arthrotomy, then it is displaced and fixed with a coracoscapular screw. Burkhart *et al*[51] reported that no recurrent instability was detected at a mean follow-up of 4.9 years following coracoid transfer performed in forty-seven patients. The Latarjet procedure, also as a revision to manage recurrence of anterior shoulder instability after previous operative repair associated with defects of the anterior glenoid rim and an intact subscapularis muscle, was reported as satisfactorily restoring glenohumeral stability[52]. Warner *et al*[53] and Scheibel *et al*[54] evaluated recurrence of the anterior instability following anterior glenoid augmentation by using iliac crest bone autograft and they reported no evidence of recurrent instability in their series.

Burkhart *et al*[24] used the term "engaging Hill-Sachs lesion" to describe a compression fracture on the posterosuperior aspect of the humeral head which drops over the glenoid rim in external rotation of an abducted shoulder and is associated with recurrent instability. Tenodesis of the infraspinatus into the lesion which is also called "remplissage" and bone grafting of the defect are the surgical interventions described to address the osseous defect on the humeral head. Boileau *et al*[55] reported that arthroscopic Hill-Sachs remplissage procedure in combination with Bankart repair in the treatment of patients with a large bony defect on the humeral head was an effective method. The authors also concluded that 98% of the patients had a stable shoulder joint at the latest follow-up with approximately 10 degrees of restriction in external rotation which did not significantly affect return to sports activity. An *in-vitro* study evaluating biomechanical effects of remplissage showed that in specimens with a 30% Hill-Sachs lesion it prevented engagement of the lesion[56]. Bone grafting can also be applied as another treatment option for defects of the humeral head. Osteoarticular plugs and osteoarticular humeral head allograft are the options for large diameter lesions[36,57]. Collapse or resorption of the graft should be kept in mind as an important risk factor which may lead to failure in such cases.

There are various techniques addressing different pathologies of both the soft tissues and bones which generally unite to form a complex disease process. Therefore, when dealing with the clinical management of recurrent anterior instability of the shoulder joint, one should always carefully analyze the patient-specific pathologies and consider treatment options according to the needs of every particular case. In this regard, a guideline is generally needed. Figure 7 demonstrates the algorithm that we use in the management of patients with recurrent anterior instability of the shoulder joint.

CONCLUSION

Anterior shoulder instability is among the most commonly seen disorders in traumatology, which typically affects the younger age population with high rates of recurrence. Recurrent anterior instability of the shoulder is a complex disease which may include both soft tissue and osseous pathologies. Primary clinical approach should be the combination of a careful medical history, a detailed physical examination, and appropriate imaging studies to recognize changes leading to recurrence. Although various surgical techniques have been described, a consensus does not exist and thus, surgeons should select the most effective procedure to restore joint stability in a patient-specific manner.

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Evaluation of anatomical considerations in the posterior maxillae for sinus augmentation

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Abstract

The edentulous posterior maxilla is considered a clinical challenge during dental implant treatment for many dental practitioners. This is because its insufficient bone quality, deficient alveolar ridge, spiny ridges, undercuts, and sinus pneumatization are often encountered after tooth loss. To overcome these problems, several approaches have been developed and are currently used, including sinus augmentation and bone augmentation. Today, two main procedures of sinus floor elevation for dental implant placement are in use: a two-stage technique using the lateral window approach, and a one-stage technique using a lateral or a crestal approach. In this study, we deal with the anatomic relations of the structures of the maxillary sinus during sinus augmentation. These anatomical findings can help in complications and potential injuries of the maxillary sinus procedures. It can be suggested that pre-operative evaluation is helpful for diagnosis and treatment planning and minimizing complication during the surgery.

Key words: Anatomy; Intraoperative complications; Sinus floor augmentation

Core tip: The edentulous posterior maxilla is considered a clinical challenge during dental implant treatment. Sinus augmentation and bone augmentation are used to overcome these problems. Maxillary sinus septa have been related to increased risk of perforation of the membrane during sinus augmentation. The lateral window design may be modified by the making of two windows or one w-shape window if the septum is lower. The branches of the maxillary artery should be taken into consideration to avoid bleeding complications. It can be suggested that pre-operative evaluation is helpful for diagnosis and treatment planning and minimizing complication during the surgery.

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INTRODUCTION

For many dental practitioners, the edentulous posterior maxilla is considered a clinical challenge during dental implant treatment[1]. This is because its insufficient bone quality, deficient alveolar ridge, spiny ridges, undercuts,

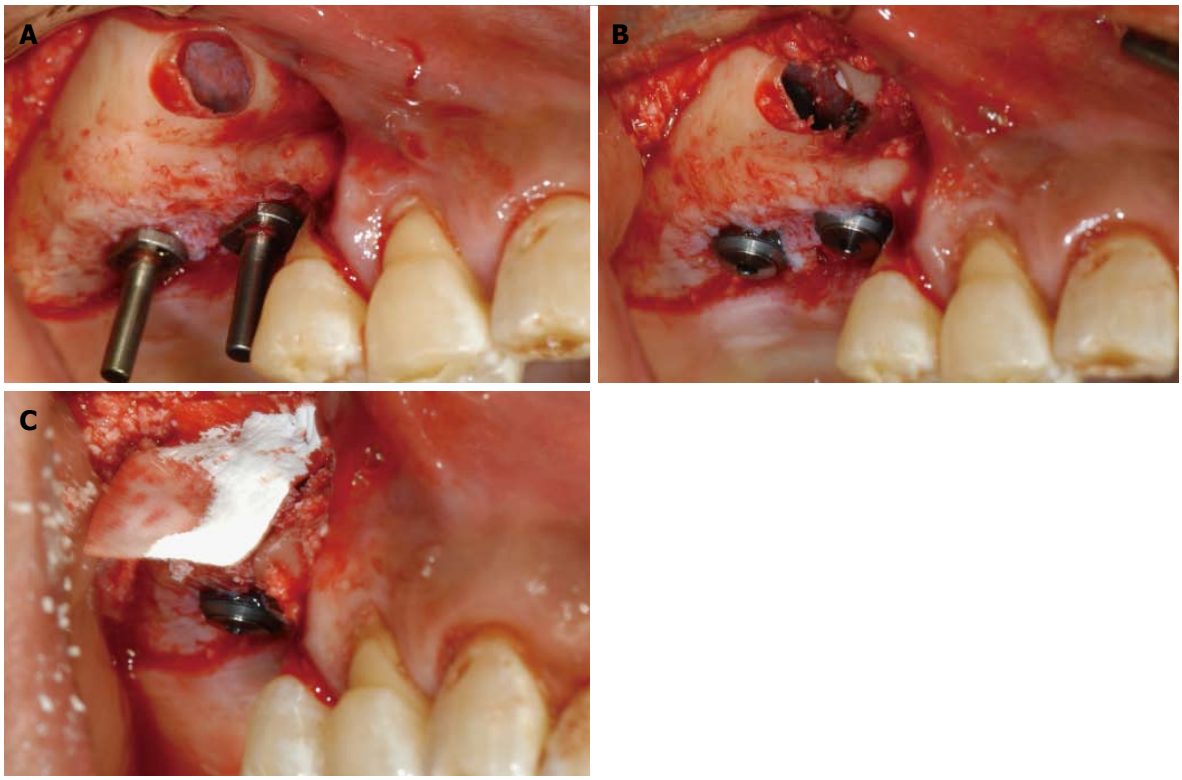

Figure 1 Buccal and clinical view. A: Buccal view after elevation of sinus membrane; B: Buccal view after installation of dental implants; C: Clinical view after application of graft material.

and sinus pneumatization are often encountered after tooth loss. Several approaches have been developed and are currently used to overcome these problems, two of them being sinus augmentation and bone augmentation[2,3]. Elevation of the maxillary sinus floor was first published by Boyne *et al*[4] in 1980. After these reports, several techniques were reported for successful sinus floor elevation, including crestal and transalveolar approaches[5,6]. A crestal approach uses the osteotome technique introduced by Summers in 1994[5]. Today, dental practitioners use two main procedures of sinus floor elevation for dental implant placement: a two-stage technique using the lateral window approach, and a one-stage technique using a lateral or a crestal approach (Figure 1)[7].

In this report, we have reviewed anatomical consideration in the posterior maxillae for sinus augmentation, to ensure predictable sinus graft surgery and help decide surgical technique with minimum complication. Preoperative evaluation seems necessary for implant surgery to succeed without complication.

ANATOMY OF MAXILLARY SINUS

Before performing sinus augmentation surgery, it is crucial to understand the anatomy of maxillary sinus. The function of the maxillary sinus is not yet well known. Theories on its physiologic function include: (1) weight reduction to maintain equipoise of the head; (2) protection of intracranial structures; (3) thermal insulation of vital parts; (4) humidification and warming of inhaled air; (5) secretion of mucus to moisten the nasal cavity; (6) secretion of mucus to moisten the nasal cavity; (7) increasing the area for olfaction; and (8) imparting resonance to the voice[8].

The maxillary sinus is the largest and most constant of the paranasal sinuses. After birth, it undergoes two periods of rapid growth, first between birth and 3 years since, and then between ages 7 and 18 years[9]. The maxillary sinus has a pyramidal shape, with an anterior wall corresponding to the facial surface of the maxilla. Its posterior bony wall separates it from the pterygomaxillary fossa medially and from the infratemporal fossa laterally. Its medial wall is the lateral nasal wall and separates the sinus from the nasal cavity and communicates with the nasal cavity *via* the ostium semilunaris to the hiatus semilunaris (middle meatus)[10]. The ostium of the maxillary sinus is high up on the medial wall and on average is 2.4 mm in diameter[10].

The Maxillary sinus floor consists of the alveolar process of the maxilla. The sinus floor is usually convex, with its lowest point around the first and second upper molars[11]. As aging occurs, the sinus floor tends to resorb and form dehiscences around the roots[12]. The root ends may jut into the cavity, covered only by the Schneiderian membrane and a small bone cortex flap[13].

SINUS PNEUMATIZATION AND RESIDUAL BONE RESORPTION

Maxillary sinus pnematization is a physiologic process

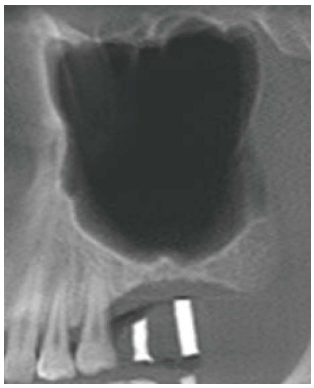

Figure 2 Panoramic view from cone beam computed tomography showing septum.

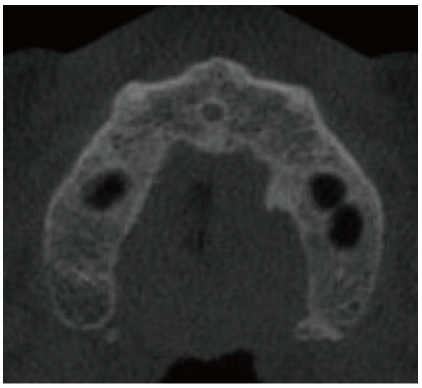

Figure 3 Axial view from cone beam computed tomography with septum on left maxillary sinus.

that occurs in all paranasal sinuses during the growth period, causing them to increase in volume[14]. The reasons for sinus pneumatization are poorly understood, but factors that cause this process include heredity, the pneumatization drive of the nose's mucous membrane, craniofacial configuration, density of the bone, growth hormones, sinus air pressure, sinus surgery, and posterior tooth extraction[15]. According to a radiographic study, pneumatization was more significant after extraction of teeth enveloped by a superiorly curving sinus floor, extraction of several adjacent posterior teeth, and extraction of second molars as opposed to first molars[15].

Residual ridge resorption following tooth extraction is unavoidable process in posterior maxillary area. Extensive ridge resorption is one of the many problems for implant-prosthetic treatment in the posterior maxillae. Although resorption rate is subject to individual variability and almost resorption occurs in 6 mo after extraction, the alveolar ridge resorption persists for subsequent years to decades[16,17].

Available alveolar bone may be compromised in the in the posterior maxillae may be compromised because of sinus pneumatization and/or residual ridge resorption after tooth loss. The average height of the available bone in the edentulous maxilla was classified into three classes[14]. Class 1 had a residual bone height of 10 mm, usually found in edentulism of no more than 5 years' standing. Class 2 had a residual bone height of 5-10 mm, usually found in edentulism of 5-10 years. Class 3 indicated a bone height of 0-5 mm, usually found in edentulism of more than 10 years. A previous report has recommended that sinus augmentation be performed in classes 2 and 3. If the implant with 10 mm length is planned, sinus augmentation should be considered in Classes 2 and 3.

SEPTA OF THE MAXILLARY SINUS

Maxillary sinus septa are barriers of cortical bone that divide the maxillary sinus into multiple compartments, known as recesses. Diagnosis of septa presence by computed tomography is important for planning maxillary sinus elevation surgery and later separating the sinus membrane from the septa (Figures 2 and 3)[18]. Septa have become increasingly important in maxillary sinus anatomy as surgical technique has developed. The cause of antral septa has been described previously[19]. Congenital septa are thought to have evolved during the growth of the middle part of the face, and the other, secondary septa are reported to be arisen from irregular pneumatization of the sinus floor after tooth extraction. Other reports classify septa as primary septa if they are located above the maxillary tooth and as other septa if they are located above an edentulous ridge, since septa may be either primary or secondary, or a combination of both types[20,21].

A previous report has showed that septa are significantly higher in the atrophic sinus than in the dentate maxillae, and septa are more commonly located in the molar regions than in the premolar and retromolar areas[22]. Prevalence of sinus septa is between 20% and 35%[19,23], and the mean height of septa is 7.5 mm[22]. Diagnosis using two-dimensional panoramic radiographs yields incorrect results in 29% of cases, and it has been suggested that three-dimensional computed tomography may be used to avoid complications during sinus augmentation[22].

The septum has been related to increased risk of perforation of the membrane during sinus augmentation[24,25]. The lateral window design may be modified by the making of two windows or one w-shape window if the septum is lower (Figure 4). Septa may be cut with a chisel and be removed so that the graft can be placed without interruption[20].

VASCULAR SYSTEM OF THE MAXILLARY SINUS

The blood supply of the maxillary sinus is derived from three arteries: the infra-orbital artery, the posterior lateral nasal artery, and the posterior superior alveolar artery[26,27]. Among these arteries, the posterior superior alveolar artery and the infra-orbital artery supply the buccal part of the maxillary sinus, and they also supply local oral mucosa as well as the mucous membrane in a double

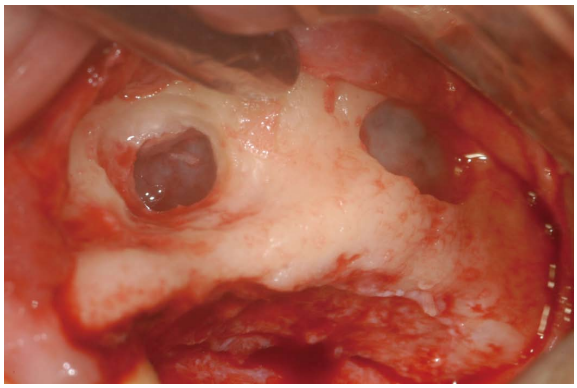

Figure 4 Buccal view showing lateral window design having two windows.

arterial circle[28]. The posterior superior alveolar artery enters the pterygopalatine fossa, and divides into one extraosseous and one intraosseous branch, which enter the maxillary tuberosity[29]. To prevent damage to the extraosseous anastomosis, it is crucial to analyze its height from the cortical bone, its diameter, and the course of the artery. The anastamosis forms a concave arch at the first molar, and that is the lowest point of the bony canal's arch course, and the mean distance between the bone crest and the canal is 19 mm[26,30]. An intraosseous vascular canal at the lateral antral wall has been found in over 50% of cases[28]. To avoid bleeding complications, the branches of the maxillary artery should be taken into consideration.

SCHNEIDERIAN MEMBRANE

The Schneiderian membrane lines the inner walls of the sinus, which is represented by ciliated columnar cells, goblet cells, and basal cells resting on the basement membrane[10]. The membrane's thickness varies but is generally 0.3-0.8 mm in unfixed, fresh cadavers without sinusitis[31]. A study with cone beam computed tomography has showed that individuals vary greatly in the thickness of their Schneiderian membranes, from 0.16 to 34.61 mm, and the highest mean values have been found in the midsagittal aspect[32]. Other local or systemic factors that influence the thickness of the Schneiderian membrane are described in previous reports. Gingival thickness and sex are reported to be related to the Schneiderian membrane's thickness: the membrane is thicker in patients with thick gingival biotype and thinner in female subjects[32-34]. Higher Schneiderian membrane thickness has been noted next to restored teeth and periodontal and endodontic lesions. Especially in molar regions with periodontal destruction, the Schneiderian membrane has thickened, particularly when there are small bone layers above the root tips or periapical lesions. In addition, inflammation or allergic phenomena, as well as smoking, are correlated with increased mucosal thickness[35].

It has been shown that the Schneiderian membrane swells significantly, by 6.7 mm, after sinus augmentation, and that this swelling disappears three weeks later[36]. In one report, patients' computed tomographic scans have been compared before bone grafting and 4 to 6 mo after bone grafting[37]. Sinus membrane thickness differs significantly before (0.8-1.2 mm) and after (1.5-1.3 mm) augmentation surgery, with a mean increase of 0.8-1.6 mm (maximum: 4.4 mm), and only 28% of augmented sinuses do not show membrane thickening. Other reports, however, show no significant change in the membrane thickness between computed tomographic scans taken before operation and an average of 8.9 mo after operation[38]. This discrepancy may be explained by the study design: the latter study excluded bilateral sinus augmentations and had higher membrane thickness before operation, with a higher history of periodontitis (75.7 %).

Which types of mucosal thickening require therapy is still unknown, but historically 2 mm is considered a reliable threshold for pathological mucosal swelling[39]. Since the most frequent surgical complication occurring during sinus augmentation is perforation of the Schneiderian membrane (10%-56%)[40], it is crucial to check the Scheniderian membrane status by cone beam computed tomography or with an endoscope, and to eliminate sinusitis and other potential pathological conditions before any surgery. A previous study shows that 38.2% of presumably reversible ear, nose, and throat contraindications have been detected and resolved before sinus augmentation, and the same study suggests that a careful multitasking preoperative management, including an ear, nose, and throat assessment with fiberoptic endoscopy and a radiological evaluation extended to the ostiomeatal complex, may be very useful in candidates for sinus augmentation[41].

CONCLUSION

In this report, we have dealt with the anatomic relations of the structures of the maxillary sinus during sinus augmentation. These anatomical findings can help with complications and potential injuries in procedures involving the maxillary sinus. It can be suggested that preoperative evaluation is helpful for diagnosis and treatment planning, as well as for minimizing complications during surgery.

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MINIREVIEWS

Value of temporary stents for the management of perivaterian perforation during endoscopic retrograde cholangiopancreatography

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Abstract

Endoscopic retrograde cholangiopancreatography (ERCP) has become the mainstay of treatment in hepato-pancreato-biliary disease. However, ERCP requires a high level of technical skills and experience in therapeutic endoscopy, there is always a risk of complications. Especially, the perforation per se affects the patient adversely, and the clinical course may lead to a poor prognosis, even with appropriate management. The treatments for ERCP-related perforation are diverse, depending on the location and mechanism of the bowel perforation and the time of diagnosis. Thus, we reviewed the appropriate surgical and non-surgical management options for therapeutic ERCP-related perforations, especially, evaluating metallic stenting as a treatment modality in perivaterian perforation.

Key words: Endoscopic retrograde cholangiopancreatography; Perforation; Self-expandable metallic stent; Duodenum; Perivaterian

Core tip: Although the evidence supporting the use of fully covered self-expandable metallic stent in perivaterian perforations is still insufficient, the clinical outcomes were encouraging.

Lee SM, Cho KB. Value of temporary stents for the management of perivaterian perforation during endoscopic retrograde cholangiopancreatography. *World J Clin Cases* 2014; 2(11): 689-697 Available from: URL: http://www.wjgnet.com/2307-8960/full/v2/i11/689.htm DOI: http://dx.doi.org/10.12998/wjcc.v2.i11.689

INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) has become the mainstay of treatment in hepato-pancreato-biliary disease since its introduction in 1968[1]. In the past, ERCP had been used as a *diagnostic* tool in choledocholithiasis presenting with jaundice, dilated common bile duct, acute pancreatitis, and cholangitis, but recently ERCP combined with sphincterotomy and stone removal has become a valuable *therapeutic* procedure[2].

Because ERCP requires a high level of technical skills and experience in therapeutic endoscopy, there is always a risk of complications, such as bleeding, perforation, pancreatitis, and cholangitis. Indeed, complication rates range from 5.4% to 11.2%[3-11], among which the rate of perforation, a potentially fatal complication, is 0.3%-1.0%[3,12,13], and the rate of mortality in perforated patients is high (8%-23%)[3,12-14]. Moreover, perforation *per se* affects the patient adversely, and the clinical course may lead to a poor prognosis, even with appropriate management. Delayed diagnosis and management can further affect clinical outcomes adversely[15,16].

The treatments for ERCP-related perforation are diverse, depending on the location and mechanism of the

Table 1 Classification of endoscopic retrograde cholangiopancreatography-related perforations

Ref.	Type
Stapfer *et al*[18]	Type Ⅰ, duodenal perforation of medial or lateral wall Type Ⅱ, perivaterian perforation Type Ⅲ, perforation of distal bile duct Type Ⅳ, retroperitoneal air alone
Howard *et al*[17]	Group Ⅰ, guidewire perforation Group Ⅱ, periampullary retroperitoneal perforation Group Ⅲ, duodenal perforation remote from the ampulla

bowel perforation and the time of diagnosis[17,18]. Previously, most ERCP-related perforations, regardless of the above factors, were managed using surgery, and the mortality rate with such surgery was generally high. However, after the introduction of treatment strategies according to the type of perforation, nonsurgical management, such as radiologic interventions using percutaneous transhepatic biliary drainage (PTBD) and endoscopic management using endoscopic nasobiliary drainage (ENBD), endoscopic retrograde biliary drainage (ERBD), endoclips, and fibrin glue, have been developed. Consequently, treatment outcomes have improved greatly over time[12,15-24].

Now, nonsurgical techniques are being used in suitable select patients more than often than surgery. Among the various nonsurgical options, several recent studies have reported that fully covered self-expandable metallic stents (SEMSs) could be used in ERCP-related perforation, especially in periampullary perforations[25-28]. Thus, we reviewed the appropriate surgical and non-surgical management options for therapeutic ERCP-related perforations, especially, evaluating metallic stenting as a treatment modality in perivaterian perforation.

CLASSIFICATION OF ERCP-RELATED PERFORATION

The treatment modality in ERCP-related perforations is associated with the type of the perforation (Table 1). Stapfer *et al*[18] classified perforations into four types according to anatomical location and severity. Type Ⅰ duodenal injuries are perforations of the lateral or medial wall, caused by the endoscope itself. Type Ⅱ duodenal injuries are perforations of the medial wall. These are perivaterian or periampullary perforations, and most occur during endoscopic sphincterotomies. Type Ⅲ duodenal injuries are perforations of the distal bile duct, typically due to wire or basket instrumentation. Type Ⅳ duodenal injuries are diminutive retroperitoneal perforations due to excessive use of compressed air to retain a patent bowel lumen.

Similar to Stapfer's classification, Howard *et al*[17] reported three types of ERCP-related perforations in accordance with the mechanism of injury. Group Ⅰ perforations are guidewire perforations of the duct, group Ⅱ perforations are periampullary perforations, and group Ⅲ perforations are duodenal perforations remote from the ampulla.

Regarding incidence by type of perforation, generally, periampullary perforations caused by endoscopic sphincterotomies are most common, 15%-55%[12,17-19]. Polydorou *et al*[23] reported incidences using a modified classification of ERCP-related perforation. Type Ⅰ, and type Ⅱ injuries are identical with Stapfer's type Ⅰ and Ⅱ injuries, but type Ⅲ injuries are ductal or duodenal perforations caused by endoscopic instruments, but not guidewires, and type Ⅳ injuries are guidewire perforations with the presence of retroperitoneal air on X-ray examination. They showed incidences of 68% for type Ⅱ, 16% for type Ⅰ, 11% for type Ⅲ, and 4% for type Ⅳ perforations. Another study showed that guidewire-related perforations were most common (32%)[19]. Moreover, 15% were sphincterotomy-related perforations, 11% occurred during passage of the endoscope, and 9% occurred due to stent migration. Morgan *et al*[22] reported that 12 of 24 cases of ERCP-related perforations were related to sphincterotomy, and the other 12 cases were perforations remote from the papilla. Although the incidence of ERCP-related perforations varied slightly among the previous studies, sphincterotomy-related perforations tend to be most common, followed by guidewire-related perforations and free wall perforations.

RISK FACTORS FOR ERCP-RELATED PERFORATIONS

Several studies have reported risk factors for ERCP-related perforations. Overall risk factors, regardless of the type of ERCP-related perforation, include old age and a longer ERCP procedure time. Enns *et al*[12] demonstrated that patients older than 65 years had a greater risk of ERCP-related perforation. Longer procedure times are often accompanied by repeated cannulation or more invasive methods to achieve "good" results. Thus, there tends to also be a greater risk of perforation. Additionally, ERCP-related perforation may be increased when performed by a trainee endoscopist. However, experts in the therapeutic ERCP field operate frequently and especially with severe and difficult cases; thus, there is always a risk of perforation during the procedure regardless of the surgeon's experience.

Risk factors for Stapfer's type Ⅰ perforation are abnormal anatomical structures, such as gastrojejunostomy, pancreaticoduodenectomy, duodenal diverticulum or stricture, and situs inversus[22,29-31]. With anatomical features that differ from those of normal situations, it may be difficult to penetrate the bowel lumen using a side-viewing endoscope, increasing the risk of perforation by the endoscope itself.

Risk factors for Stapfer's type Ⅱ, Ⅲ, and Ⅳ perforations are similar and overlapping. They include sphincter of Oddi dysfunction, precut sphincterotomy, and a dilated common bile duct on abdominal imaging[12]. Precut sphincterotomy has been reported as a known risk factor

for pancreatitis[6,7,32]. However, several studies have demonstrated that precut sphincterotomy also increases the risk of perforation compared with a conventional sphincterotomy. In fact, the risk of perforation increases if the incision for the sphincterotomy is outside of the usually recommended sector (11 to 1 o'clock position)[6,33-35]. A previous report demonstrated that 7 of 13 sphincterotomy-related perforations were associated with precutting[12]. Since a dilated common bile duct is associated with distal common bile duct stricture, the risk of perforation may be related to the deep manipulation needed to achieve a deep cannulation. Additionally, an ampullectomy can increase the risk of perforations. Alfieri *et al*[15] reported that ampullectomy had been performed in 7 of 30 (23%) cases of ERCP-related perforations.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Patients with ERCP-related perforations may complain mainly of epigastric pain and tenderness, but obviously these complaints are very nonspecific. Other symptoms and signs include fever, tachycardia, leukocytosis, and mildly elevated serum amylase levels. Several studies have reported rare complications after ERCP, such as pneumomediastinum, pneumothorax, and gas in the portal system[36-42], whereas patients with retroperitoneal air present on abdominal imaging, after an endoscopic sphincterotomy, can be asymptomatic clinically. Generally, the patients did not require intervention but only conservative management. Genzlinger *et al*[43] showed that asymptomatic patients with retroperitoneal air evident on a computed tomography (CT) scan did not require surgical intervention. As the range is diverse, from asymptomatic to severe signs of peritonitis, to suspect and recognize the possibility of perforation early, during and after ERCP is most important. For early detection of perforation, it is necessary to check the patient's condition immediately after ERCP. If the patient complains severe abdominal pain, abdominal X-ray and CT are good methods to identify ERCP-related perforation. If retroperitoneal air is visible during the procedure, abdominal X-ray and CT are also useful.

ERCP-related perforation can sometimes be diagnosed readily by imaging if suspected. Typically, an abdominal X-ray may show retroperitoneal air around the right kidney. Suspected perforation may not be confirmed by an abdominal X-ray, but a contrast CT scan or upper gastrointestinal oral contrast evaluation should be helpful. However, this could be delayed unless the physician suspects a perforation. Furthermore, if the patient has elevated serum amylase levels and complaints of epigastric pain, it is difficult to distinguish between perforation and pancreatitis. Gottlieb *et al*[44] reported that post-ERCP pancreatitis can be excluded if their values of amylase and lipase 2 h after ERCP are below 276 U/L and 1000 U/L, respectively. Another study demonstrated that post-ERCP pancreatitis cases showed serum amylase levels greater than five-fold the normal level[45]. Thus, laboratory findings, especially serum amylase and lipase levels, may be important clues for differentiating perforation from pancreatitis.

Although a physical examination is frequently useful in suspected patients, not all perforated patients show signs of acute peritonitis[43]. Bell *et al*[46] demonstrated positive physical findings in 75% of the included patients, but no specific finding of perforations. Thus, it is important to consider not only a physical examination and laboratory findings but also abdominal imaging, such as abdominal X-ray and abdominal CT scans, for an accurate diagnosis.

TREATMENT OF ERCP-RELATED PERFORATION

Traditionally, ERCP-related perforation has been managed surgically. The objectives of such surgical management include control of infection and inflammation (drainage of the retroperitoneal/intraperitoneal fluid and air and drainage of the biliary system) and closure of the perforation, with or without bypass[2]. However, the recent trend has been towards a selective approach according to the type of perforation and, more recently, according to the overall status of the patient, considering issues such as age, vital signs, peritoneal signs, comorbidities, and CT images.

Duodenal free wall perforations (Stapfer type I or Howard Group Ⅲ) tend to be larger and located remotely from the ampulla and to cause substantial collections in the peritoneal or retroperitoneal space. Thus, these perforations should be subjected to prompt surgical intervention. One study reported three of four cases of type I perforation that underwent surgery immediately[12]. One case had abnormal anatomy, a gastrojejunostomy, and the others cases had duodenal diverticulum and stricture. All three patients were suspected and diagnosed immediately; there was no mortality. The one patient without surgical management had severe comorbidities, thus receiving only conservative management but died 2 d later. Polydorou *et al*[23] reported that 83% (6/7) of Stapfer's type I perforation cases underwent surgery. Three patients with type I perforation showed abnormal anatomy due to Billroth Ⅱ gastrectomies. Among the patients who underwent surgery, two died as a result of respiratory insufficiency and aspiration pneumonia. One patient with a type I perforation, caused by rupture of the diverticulum, was managed conservatively. The patient had no fever or signs of peritonitis but only complained of mild abdominal pain.

In the studies mentioned above, in general most of the type I perforations were treated using surgery due to the large size of the perforation. Recently, some studies have introduced endoscopic management using simple metallic endoclips or an endoloop with multiple endoclips and fibrin glue for free wall duodenal perforations[28,34,47-50]. In addition, an over-the-scope-clip, used

Table 2 Treatment of periampullary perforations (Stapfer's type II perforations)

Ref.	Patients (*n*)	Patients according to treatment method, *n* (%)	Treatment method	Mortality *n* (%)
Alfieri *et al*[15]	15	6 (40.0)	Conservative management + ENBD ± PTBD	0 (0.0)
		9 (60.0)	Surgery	1 (11.1)
Wu *et al*[16]	11	6 (54.5)	Conservative management	0 (0.0)
		5 (45.5)	Surgery	4 (80.0)
Kim *et al*[58]	5	2 (40.0)	Conservative management	0 (0.0)
		3 (60.0)	Surgery	0 (0.0)
Enns *et al*[12]	13	11 (84.6)	Conservative management ± biliary drainage (PTBD, ERBD)	0 (0.0)
		2 (13.4)	Surgery	0 (0.0)
Polydorou *et al*[23]	30	24 (80.0)	Conservative management ± biliary drainage (PTBD, ERBD)	0 (0.0)
		6 (20.0)	Surgery	0 (0.0)
Stapfer *et al*[18]	6	3 (50.0)	Conservative management	0 (0.0)
		3 (50.0)	Surgery	0 (0.0)
Howard *et al*[17]	22	18 (81.8)	Conservative management ± biliary drainage (ENBD, ERBD)	0 (0.0)
		4 (18.2)	Surgery	1 (25)
Morgan *et al*[22]	12	12 (100.0)	Conservative management	0 (0.0)
		0 (0.0)	Surgery	0 (0.0)
Kim *et al*[59]	9	8 (88.8)	Conservative management ± ENBD	0 (0.0)
		1 (11.2)	Surgery	0 (0.0)

Conservative management: intravenous antibiotics, fluids, pain control, nil-by-mouth, close monitoring, and nasogastric drainage. ENBD: Endoscopic nasobiliary drainage; PTBD: Percutaneous transhepatic biliary drainage; ERBD: Endoscopic retrograde biliary drainage.

primarily in gastrointestinal bleeding or perforation, could be considered for use in post-ERCP perforations[51,52].

Distal bile duct injuries (Stapfer type Ⅲ or Howard Group Ⅰ), caused by penetration of the guidewire through the bile duct during cannulation in a narrow or obstructed duct, tend to be smaller than duodenal free wall perforations. Commonly, these perforations tend to become obstructed spontaneously, and these patients can be 'cured' by conservative management with intravenous antibiotics, hydration, pain control, or nil-by-mouth[12,17,18,53]. However, since some patients have ongoing bile leakage, endoscopic management to prevent bile leakage to the retroperitoneum may be necessary. To prevent such leakage, ENBD or ERBD together with insertion of a plastic or metallic stent can be used. If endoscopic management is not possible, PTBD can be performed.

Diminutive duodenal perforation (Stapfer type Ⅳ) is not a true perforation; generally, it can be treated sufficiently with conservative management alone. In fact, Genzlinger *et al*[43] reported that retroperitoneal air alone, with no abnormal clinical signs or symptoms, does not require surgical intervention. However, regardless of the type of perforation, patients with retained stones or unalleviated biliary obstruction should undergo surgery[18].

Perivaterian perforations (Stapfer type Ⅱ or Howard group Ⅱ) occurring after endoscopic sphincterotomy are controversial issues in the treatment field presently because of variation in clinical outcomes[14,18,34,41,53-57]. Surgical intervention is not an issue but is an abstruse problem, because it seems that conservative management alone, including biliary drainage, may aggravate or fail to cure the perforation. Several studies have demonstrated that conservative management with or without biliary drainage was successful in peri-ampullary perforation patients[18,53-55].

Wu *et al*[16] reported that 55% (6/11) of patients with type II perforations were treated with conservative management with or without biliary drainage. In all patients, clinical signs and symptoms improved rapidly. However, 80% (4/5) of the patients who underwent surgery died, due to delayed diagnosis and operation as well as sepsis. The surgical indications for those patients were large retroperitoneal fluid collections, liver abscess on abdominal CT scan, and severe abdominal pain. Enns *et al*[12] demonstrated that 46% (6/13) of patients with type II perforations were treated using conservative management with or without nasogastric suction. In 38% (5/13) of the patients, biliary drainage (stent insertion with three, PTBD with two) was performed. The mortality rate was zero in patients managed conservatively and with biliary drainage. Alfieri *et al*[15] showed that 40% (6/15) of patients with type Ⅱ perforations were treated successfully by conservative management with biliary drainage (PTBD or nasobiliary drainage).

The rates of nonsurgical management *vs* surgical intervention in peri-ampullary perforation vary widely (Table 2)[12,15-18,22,23,58,59]. Thus, the appropriate choice of treatment modality for peri-ampullary perforation remains an important issue. Most surgical indications in peri-ampullary perforations include hemodynamic instability, signs of peritonitis, continuing leakage, septic conditions, and a perforation of large size. One author also suggested that patients with a large amount of fluid collection in the peritoneum or retroperitoneum on abdominal CT should be treated aggressively[12], because the possibility of continuing leakage is high. If there is no surgical indication, the essential aspects of nonsurgical management consist of diversion of duodenal, biliary, and pancreatic drainage[21]. A nasogastric or nasoduodenal tube for duodenal

Table 3 Temporary self-expandable metallic stent used for peri-ampullary perforations

Ref.	Age/sex	ERCP indication	Abdominal CT scan	Stent indication	Type of stent/duration (d)
Vezakis *et al*[28]	61/F	Stones or sphincter of Oddi dysfunction	Retroperitoneal air	Duodenal fistula, Continuing leakage	Partially covered SEMS/14
Jeon *et al*[26]	82/F	Stones	Retroperitoneal air and fluid	Continuing leakage	Fully covered SEMS/28
Canena *et al*[25]	55/F	Stones	Retroperitoneal air and fluid	Perforation	Fully covered SEMS/21
	29/F	Stones	Retroperitoneal air and fluid	Perforation	Fully covered SEMS/30
	31/M	Stones	Retroperitoneal air and fluid	Perforation	Fully covered SEMS/30
	76/F	Stones	Retroperitoneal air and fluid	Perforation	Fully covered SEMS/29
Park *et al*[27]	61/F	Biliary tree dilatation	Retroperitoneal air and fluid	Perforation	Fully covered SEMS/10
Unpublished	46/M	Stones	Retroperitoneal air	Perforation	Fully covered SEMS/ spontaneously fell out

CT: Computed tomography; SEMS: Self-expandable metallic stent; ERCP: Endoscopic retrograde cholangiopancreatography.

decompression can be used. ENBD or ERBD can be used in internal biliary drainage to prevent leakage of bile juice into the perforation site. For external biliary drainage, PTBD is used as well.

However, some conditions, such as severe common bile duct dilatation or a large perforation hole, may reduce the diversion of biliary drainage using ENBD or ERBD[27]. Thus, several studies have reported that fully covered self-expandable metallic stents (SEMS) can be useful in biliary stenting for perivaterian perforations[25-28].

Initially, most periampullary perforation patients receive conservative management with or without biliary drainage, according to most previous studies. If conservative management failed and a delayed operation was then performed, the subsequent clinical course was found to be poor in some studies[15,16]. Thus, there is a need to treat using active conservative management. Taking advantage of biliary drainage by ENBD, ERBD, use of plastic or metallic stents, PTBD, duodenal drainage *via* a nasogastric or nasoduodenal tube, pancreatic drainage, and inflammation control are essential. "Conservative management" indicating only intravenous antibiotics, hydration, pain control, and nil-by-mouth is inadequate. Indeed, it is important to combine methods to prevent bile leakage into the perforation site.

ARE FULLY COVERED SEMS IN ERCP-RELATED PERFORATIONS VALUABLE?

As mentioned above, it is important to divert biliary drainage to prevent leakage of bile juice into the peritoneum in a peri-ampullary perforation. For such diversion, fully covered SEMS occlude the perforation site by radial force, and the perforation site can heal quickly. That is, recovery of the epithelium in the injury site, stent-associated reepithelialization, is achieved. A similar procedure has been performed previously in esophageal perforations. Siersema *et al*[60,61] reported that a fully covered SEMS was useful in nonmalignant and traumatic esophageal perforations; however, in general fully covered SEMS have been used for malignant perforations or fistulas for palliative management. A fully covered SEMS enabled the sealing of an esophageal perforation and prevented mediastinal infection.

Some case series have reported the use of SEMS in ERCP-related perforations (Table 3)[25-28]. Vezakis *et al*[28] reported a case of a persistent high-volume duodenal fistula, caused during an endoscopic sphincterotomy, that was treated successfully using a partially covered SEMS. Jeon *et al*[26] also reported the use of a fully covered SEMS in a sphincterotomy-related duodenal perforation. Although this patient had retroperitoneal fluid collections and peritonitis, she was not considered a candidate for surgery. She was treated with multiple plastic stents for internal biliary drainage and with PTBD for external biliary drainage due to her poor medical condition and old age (82 years). However, because of persistent percutaneous catheter drainage (> 150 mL/d) and contrast leakage from a distal common bile duct on tubogram, a fully covered SEMS was inserted after removing the previous plastic stents. She then recovered completely, and the fully covered SEMS was removed 1 mo later.

Park *et al*[27] also considered duodenal perforation after endoscopic sphincterotomy, similar to the above two studies. Their case was a 61-year-old female complaining of right upper quadrant pain. Biliary duct dilatation had been detected on an abdominal CT scan, and therefore ERCP with sphincterotomy was performed. The day after ERCP, she developed severe abdominal pain, fever, and leukocytosis according to laboratory findings. An abdominal CT showed retroperitoneal air and fluid collection, and the diagnosis was peri-ampullary perforation. A fully covered SEMS (5-cm-long, 10 mm in diameter) was inserted immediately after identifying the perforation, and the patient recovered completely. The retroperitoneal fluid collection seen on the abdominal CT scan resolved. The stent was then removed 10 d after insertion.

In another previously unpublished case, a 46-year-old male was referred to the hospital for right quadrant abdominal pain. He had previously undergone a Billroth I operation for gastric ulcer perforation. Because the patient developed abnormal liver functioning and gallbladder stones on abdominal CT scan, ERCP was performed to identify the biliary duct stone. However, after endoscopic sphincterotomy, a peri-ampullary perforation was detected, and a fully covered SEMS was placed immediately during the ERCP (Figures 1 and 2). After stent-

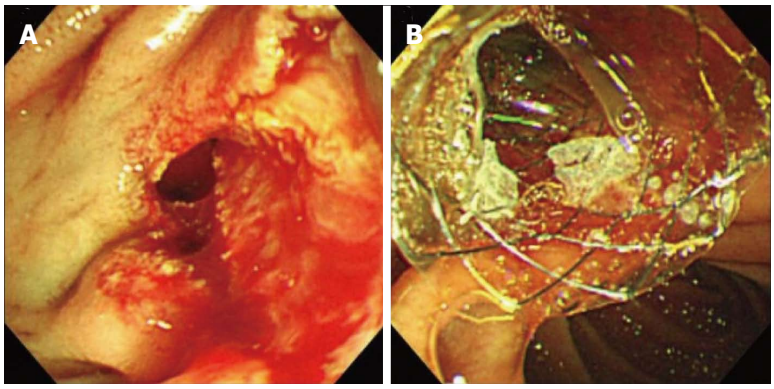

Figure 1 Insertion of fully covered self-expandable metallic stent for the management of periampullary perforation immediately after endoscopic sphincterotomy. A: A peri-ampullary perforation was seen after endoscopic sphincterotomy; B: A fully covered self-expandable metallic stent (5-cm-long, 10 mm in diameter) inserted into the common bile duct to prevent bile entering the perforation site can be seen at the ampulla of vater.

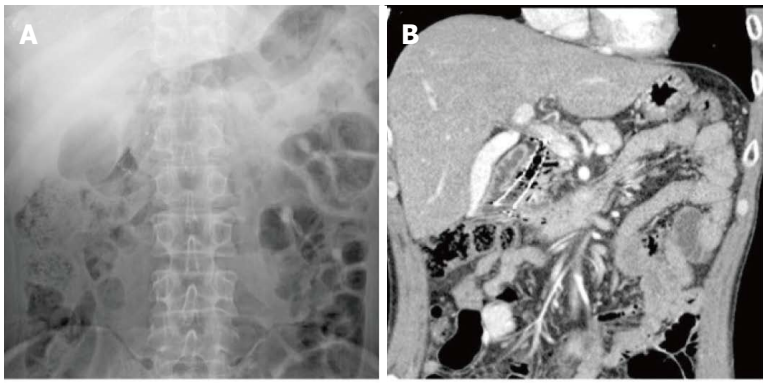

Figure 2 Deployed fully covered self-expandable metallic stent on (A) abdominal X-ray and (B) abdominal computed tomography scan.

ing, the patient was stable and was discharged without complications. Although he underwent endoscopy for removal of the stent on day 28 after insertion, the stent had already fallen out spontaneously.

Because fully covered SEMS are available in large diameters, they can be used in a dilated common bile duct without stent migration. They are capable of maintaining long-term patency of the lumen, in contrast to plastic stents. Also, in comparison with uncovered SEMS, fully covered SEMS have several benefits. Uncovered SEMS tend to embed readily in the duct, making it difficult to remove the stent[62-64]. Thus, it is inappropriate to use them for benign conditions, such as strictures, obstructions, and traumatic perforations. The fully covered SEMS overcomes these disadvantage, and can be removed readily[64-66].

However, the optimal duration of stenting has not been established. Bakken *et al*[67] reported that the mean duration of stent placement was 67 (range, 0-279) d for benign strictures and 59 (range, 1-601) d for leaks, fistulas, and perforations. Another study showed that the mean duration was 37 (range, 4-84) d for benign conditions[68]. While discrepancies exist among studies, the time until stent removal is approximately 2 mo for benign esophageal conditions. Several studies have reported stenting durations in peri-ampullary perforations ranging from 10 to 30 d[25-28]. Moreover, because the treatment outcome did not seem to depend on the duration of stenting, and the stent was removed according to the status of the patient, a stent should be removed when the patient shows improved perforation-related symptoms, signs, and imaging results, such as simple abdominal X-rays and abdominal CT scans, even after 1 wk of stenting.

Although several studies have demonstrated good outcomes using temporary fully covered SEMS in ERCP-related perforations, clinically, the situation has not been clarified entirely. Because treatment failure after non-surgical treatment, including the insertion of plastic stents and fully covered SEMS, can cause high mortality and morbidity, close attention must be paid to the decision on treatment modality. A decision taking into consideration the surgery time, while performed non-surgical treatment, is also important. Unrelieved abdominal pain, continued leakage on abdominal CT scans, or hemodynamic instability despite non-surgical management are considerations relevant to surgical intervention. Thus, frequent physical examinations and serial follow-up using abdominal CT scans are helpful in checking for adverse events or treatment failure. However, a patient's condition, such as cardiopulmonary comorbidity, hemodynamic instability, and old age, is also highly relevant to postoperative mortality. If a patient with peri-ampullary perforation has an inoperable condition due to high postoperative risks, a fully covered SEMS can be attempted for palliative treatment[26]. First, it is better to use a fully covered SEMS, especially for a major leakage and large perforation, because ENBD and ERBD may not prevent bile flow into the perforation site completely. Although it is essential to select cases according to their condition, optimal conservative management using a fully covered SEMS may be a good treatment option.

In conclusion, early diagnosis of ERCP-related duodenal perforation is important, and according to the type of perforation, its treatment varies from conservative

management to surgical intervention. Although conservative management is the mainstay for all types of perforations, except type I perforations, the most appropriate treatment modality should be established by performing a comprehensive evaluation of the patient. In particular, a fully covered SEMS for perivaterian perforations was used in selected cases, and the clinical outcomes were encouraging. However, the evidence supporting the use of fully covered SEMS in perivaterian perforations is still insufficient, and further studies are required.

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ORIGINAL ARTICLE

Simultaneous *vs* staged treatment of urolithiasis in patients undergoing radical prostatectomy

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Abstract

AIM: To assess the outcomes of men treated for urolithiasis at the time of radical prostatectomy.

METHODS: From 1991 to 2010, 22 patients were retrospectively identified who were treated simultaneously (n = 10) at radical prostatectomy, or (n = 12) within 120 d prior to prostatectomy, for urolithiasis. Clinical characteristics were reviewed including: type of prostatectomy and stone surgery, location and amount of stone burden, perioperative change in hemoglobin and creatinine, stent frequency, total hospital d, stone-free rates, additional stone procedures and complications. Long-term functional outcomes including stress urinary incontinence and bladder neck contracture were reported. Differences between cohorts (simultaneous *vs* staged treatment) were assessed.

RESULTS: Among men undergoing radical prostatectomy, primary stone procedures included 12 ureteroscopy, 6 shock wave lithotripsy, 2 open nephrolithotomy and 2 percutaneous nephrolithotomy. In staged shock wave lithotripsy there were 4 complications and 3 additional procedures *vs* 1 (P = 0.5) and 0 (P = 0.2) in the simultaneous cohort. Meanwhile in staged ureteroscopy there were 5 complications and 1 additional procedure *vs* 1 (P = 0.2) and 1 (P = 0.9) in the simultaneous cohort. Additional procedures for residual stones was greater among patients with asymptomatic upper tract calculi 3 (60%) relative to patients with symptomatic stones 2 (13%; P = 0.02). Likewise, patients with proximal or multiple calculi had a greater total hospital days 5.5 *vs* 4.1 (P = 0.04), additional procedures 6 *vs* 0 (P = 0.04) and lower stone-free rates 39% *vs* 89% (P = 0.02) relative to men with distal stones. Finally, there was no difference in the incidence of bladder neck contracture (P = 0.4) or stress urinary incontinence (P = 0.7) between cohorts.

CONCLUSION: Ureteroscopic treatment of symptomatic distal urolithiasis at radical prostatectomy appears to be safe and efficacious with a low rate of adverse postoperative outcomes.

Key words: Urolithiasis; Kidney stone; Prostate cancer; Radical prostatectomy

Core tip: Prostate cancer and urolithiasis can present simultaneously. An acute stone event in the immediate perioperative radical prostatectomy period poses unique management issues. Herein, we describe our experience with the simultaneous treatment of urolithiasis at the time of prostatectomy. We concluded that simultaneous ureteroscopy among symptomatic men with distal ureteral calculi appears to be safe and efficacious. Whereas, in asymptomatic men, or those with proximal/multiple calculi, one should consider treatment in a staged fashion secondary to an increased risk of additional procedures and lower stone-free rates.

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INTRODUCTION

The incidence of urolithiasis and associated healthcare costs continues to rise[1-5]. Specifically, the prevalence of stone disease in the male population ages 50 to 74 years old has increased from 13% from 1988-1994 to 19% in 2007-2010[2], representing a roughly equivalent to 40% relative increase in stone disease[6]. A similar increase in the incidence of prostate cancer has also been observed due to prostate-specific antigen (PSA) screening[7-11]. Currently, it is estimated that greater than 240000 patients are diagnosed with prostate cancer annually in the United States[8,9]. As such, a significant number of male patients diagnosed with prostate cancer may harbor urolithiasis.

As part of prostate cancer evaluation a subset of high-risk men undergo cross-sectional imaging to evaluate for metastatic disease[12-15]. If urinary stone disease is discovered, these patients pose a complex management dilemma given that 44% of asymptomatic patients with urolithiasis will develop symptoms within 1.3 years[16-19]. An acute stone event within the immediate post radical prostatectomy period poses a unique concern; specifically, instrumentation of the fresh vesicourethral anastomosis has the potential for anastomotic injury with resultant long-term urinary incontinence[20,21] and/or bladder neck contracture[22,23]. Historically, at our institution, such cases have been temporized with a nephrostomy tube and delayed definitive stone management until after the vesicourethral anastomosis matures (approximately 120 d).

To date, the safety and feasibility of synchronous treatment of urinary stone disease at radical prostatectomy is unknown. The goal of this study is to assess outcomes of patients with upper tract stone disease treated at the time of prostatectomy compared to those treated in the preoperative period.

MATERIALS AND METHODS

We retrospectively reviewed all male patients who underwent radical prostatectomy from 1991 to 2010. A total of 22 patients were identified who underwent radical retropubic prostatectomy (RRP) or robotic-assisted radical prostatectomy (RARP) treated simultaneously, or within 120 d preoperatively, for urolithiasis. We evaluated clinical characteristics including type of prostatectomy and stone surgery, location and amount of stone burden, perioperative change in hemoglobin and creatinine, stent frequency, total hospital days, stone-free rates, additional stone procedures and postoperative complications including: steinstrasse, intraoperative bleeding requiring transfusion, acute kidney injury[24], and urosepsis. The total length of hospital stay included both stone and radical prostatectomy procedure. Urinary incontinence was defined as bothersome leakage with straining or need for pad. Bladder neck contracture was identified during post-prostatectomy cystoscopy for obstructive voiding symptoms.

The urinary stone procedure was determined by the operating surgeon based on stone location, timing and type of radical prostatectomy. Simultaneous primary stone intervention was defined as occurring under the same anesthetic as the radical prostatectomy. Staged stone treatments were those within the 120 d before prostatectomy. Maximum stone diameter, location and total burden were determined by preoperative abdominal radiography or computerized tomography. Urolithiasis follow-up included metabolic evaluation, urinalysis with culture and kidney, ureter, and bladder (KUB) X-ray with renal ultrasound between 6-12 wk following stone treatment. Additional cross-sectional imaging, or KUB X-ray with tomograms, was obtained based upon patient symptomology and at the discretion of the treating provider. Stone-free status, after the primary stone procedure was defined as no residual fragments. Postoperative prostate cancer surveillance included physical examinations and serum PSA measurement quarterly for 2 years, semiannually for an additional 2 years and annually thereafter.

Statistical analysis was performed with Student's *t*-test or Wilcoxon Rank Sum for continuous data and Chi-Square or Fisher's Exact test for categorical outcome analysis using JMP software (SAS Institute Inc., Cary, North Carolina), with a P value < 0.05 considered statistically significant.

RESULTS

A total of 29 stone procedures were performed in 19 (86%) men undergoing RRP and 3 (14%) RARP at a median age of 65 years [Interquartile range (IQR) 62-69] (Table 1). Mean follow-up in the simultaneous cohort was 48.5 mo *vs* 45.7 mo in staged patients. In the staged cohort stones were treated prior to radical prostatectomy at a median 31 d (IQR 21-55). A prior history of urolithiasis was present in 16 (73%) men overall. At the time of stone surgery 17 (77%) men presented with one or more symptoms of flank pain, hematuria, urinary tract infection, pyelonephritis or acute renal failure. Ureteral stent was placed in 20 of 21 patients (95%) and nephrostomy tube only in 1 patient. In the simultaneous cohort, ureteral stent was removed at the time of urethral catheter removal 14 d post-prostatectomy with stent string secured to urinary catheter in 4 (40%), *via* clinic cystoscopy 21 d after procedure in 3 (30%), at the time of subsequent stone procedure in 1 (10%) or other method in 2 (20%). In staged patients, ureteral stents were all removed prior to radical prostatectomy or at the time of RRP. Follow-up imaging to determine stone-free status was obtained

Table 1 Patient demographics *n* (%)

	Simultaneous (*n* = 10)	Staged (*n* = 12)	*P*-value
Age (yr), median (IQR)	68 (60-71)	63 (62-67)	0.4[1]
Stone size (mm), mean ± SD	8.0 ± 3.8	9.9 ± 5.3)	0.3[1]
Location			
Renal	2 (20)	2 (17)	0.8[2]
Proximal	2 (20)	2 (17)	0.8[2]
Multiple	1 (10)	4 (33)	0.2[2]
Distal	5 (50)	4 (33)	0.4[2]
Procedure (n = 29)	11	18	
Open	2 (18)	0 (0)	-
Rigid URS	5 (46)	5 (28)	-
Flexible URS	2 (18)	4 (22)	-
SWL	2 (18)	4 (22)	-
PCNL	0 (0)	5(28)	-
RARP	1 (10)	2 (17)	-
RRP	9 (90)	10 (83)	-
Patient symptomatic	7 (70)	10 (83)	0.5[3]
History of stones	9 (90)	7 (58)	0.1[3]

[1]Student's *t*-test; [2]Fisher's Exact; [3]χ^2. IQR: Interquartile range; SD: Standard deviation; SWL: Shock wave lithotripsy; URS: Ureteroscopy; PCNL: Percutaneous nephrolithotomy; RARP: Robot assisted radical prostatectomy; RRP: Radical retropubic prostatectomy.

in all patients. Mean stone diameter was 9.1 mm (range 4-20 mm) with no difference in stone size or location between groups. After the initial stone procedure, 6 (60%) simultaneous and 7 (58%) staged were stone-free (P = 0.9) with no difference in stone size between stone-free patients and those with residual calculi (mean 8.3 mm *vs* 10.2 mm; P = 0.3).

Postoperative complications were noted in 5 (42%) staged and 3 (30%) simultaneous patients (P = 0.6), for a total of 7 and 3 complications (P = 0.3) (Table 2). In the simultaneous cohort, bleeding requiring transfusion occurred during radical prostatectomy in 2 (20%) and postoperative urosepsis in 1 (10%). In the staged cohort, there were 7 complications in 5 (42%) patients including 2 (17%) steinstrasse, 4 (33%) bleeding events during and 1 (8%) acute kidney injury after radical prostatectomy. Overall, bladder neck contracture occurred in 3 (14%) patients of whom all required bladder neck dilation. Stress urinary incontinence persisted in 7 (39%), with 1 (4.5%) requiring artificial urinary sphincter and 6 (27%) utilizing ≤ 1 pad with activity.

We then performed a subgroup analysis of simultaneous *vs* staged ureteroscopy (URS) and shock wave lithotripsy (SWL) and found no significant difference in outcomes between groups including: perioperative complications, bladder neck contracture, urinary incontinence, stone-free rates or number of additional procedures(Tables 3 and 4). Among patients undergoing simultaneous URS there were no stone related complications or bladder neck contractures; furthermore only 1 (17%) patient required an additional procedure. In those undergoing SWL, 4 (67%) patients experienced significant complications and 3 (50%) required additional procedures.

Table 2 Simultaneous *vs* staged urinary stone treatment at time of prostatectomy *n* (%)

	Simultaneous (*n* = 10)	Staged (*n* = 12)	*P*-value
Patient complications	3 (30)	5 (42)	0.6[1]
Steinstrasse	0 (0)	2 (17)	0.2[1]
Bleeding[2]	2 (20)	4 (33)	0.5[1]
AKI	0 (0)	1 (8)	0.4[1]
Urosepsis	1 (10)	0 (0)	0.3[1]
BNC	2 (20)	1 (8)	0.4[1]
Urinary incontinence	2 (33)	5 (42)	0.7[1]
Change in Cr (mg/dL), mean ± SD	0.04 ± 0.2	-0.2 ± 0.5	0.1[3]
change in Hb (g/dL), mean ± SD	3.9 ± 1.4	4.7 ± 1.6	0.2[3]
Hospital (d), mean ± SD	4.5 ± 3.8	5.5 ± 2.8	0.5[3]
Stone free	6 (60)	7 (58)	0.9[4]
Multiple procedures	1 (10)	4 (33)	0.2[4]
Avg. # stone procedures, mean ± SD	1.1 ± 0.3	1.4 ± 0.7	0.2[3]

[1]Fisher's Exact; [2]Occurred at the time of prostatectomy; [3]Student's *t*-test; [4]χ^2. BNC: Bladder neck contracture; AKI: Acute kidney injury; Cr: Creatinine; Hb: Hemoglobin; SD: Standard deviation.

When stratified by symptomology, 5 (23%) were asymptomatic and 17 (77%) had stone related symptoms; of which, multiple procedures were required in 3 (60%) *vs* 2 (12%; P = 0.02) respectively with no difference in adverse events or length of hospitalization. When stone location was analyzed, 9 (41%) patients had distal ureteral calculi and 13 (59%) had proximal or multiple stones. Relative to patients with multiple or proximal stones, patients with distal calculi had a significantly shorter hospital stay (mean 4.1 *vs* 5.5 d; P = 0.040) and need for subsequent procedures (mean 1.0 procedures/patient; P = 0.03). Moreover, in proximal or multiple stones, 5 (36%) patients required 6 additional procedures (mean 1.46 procedures/patient; P = 0.050) with a stone-free rate following the initial procedure of 5 (39%) *vs* 8 (89%) for distal ureteral calculi (P = 0.02). Finally, there was no difference in complications among those with distal stones compared to proximal or multiple stones [3 (33%) *vs* 5 (38%); P = 0.8].

DISCUSSION

We evaluate the feasibility, safety and efficacy of simultaneous prostate cancer and urinary stone disease treatment. The potential advantages of this approach include the minimization of perioperative complications associated with urolithiasis and the need for additional procedures. We found no significant difference in treatment outcomes among simultaneous or staged patients; including those men undergoing URS. Meanwhile, men with multiple or proximal stones were at increased risk for additional procedures, longer hospitalization and lower stone-free rates relative to those with distal stones. Similarly, asymptomatic patients were more likely to require additional procedures. Finally, men undergoing SWL had a high rate of stone related complications and retreatment making this a poor option for a simultaneous

Table 3 Simultaneous *vs* staged ureteroscopic stone treatment at time of prostatectomy *n* (%)

	Simultaneous (*n* = 6)	Staged (*n* = 7)	*P*-value
Age (yr), median (IQR)	70 (65-71)	63 (61-68)	0.06[1]
Patient complications	1 (17)	3 (43)	0.3[2]
Steinstrasse	0 (0)	0 (0)	-
Bleeding[3]	1 (17)	3 (43)	0.3[2]
AKI	0 (0)	1 (14)	0.3[2]
BNC	0 (0)	1 (14)	0.3[2]
Urinary Incontinence	2 (40)	3 (43)	0.9[2]
Change in Cr (mg/dL), mean ± SD	0.04 ± 0.1	-0.4 ± 0.5	0.1[4]
Change in Hb (g/dL), mean ± SD	4.1 ± 1.8	5.1 ± 0.9	0.2[4]
Hospital (d), mean ± SD	2.8 ± 2.1	5.5 ± 3.5	0.1[4]
Multiple procedures	1 (17)	1 (14)	0.9[4]
Avg. # stone procedures, mean ± SD	1.2 ± 0.4	1.1 ± 0.4	0.9[4]
Stone free	4 (67)	6 (86)	0.4[4]
Stone size (mm), mean ± SD	5.8 ± 1.7	6.9 ± 2.3	0.3[4]

[1]Student's *t*-test; [2]Fisher's Exact; [3]Occurred at the time of prostatectomy; [4]χ^2. BNC: Bladder neck contracture; AKI: Acute kidney injury; Cr: Creatinine; Hb: Hemoglobin; SD: Standard deviation.

Table 4 Simultaneous *vs* staged SWL at time of prostatectomy *n* (%)

	Simultaneous (*n* = 2)	Staged (*n* = 4)	*P*-value
Age (yr), median (IQR)	55 (53-57)	63 (62-65)	0.1[1]
Patient complications	1 (50)	3 (75)	0.5[2]
Steinstrasse	0 (0)	2 (50)	0.2[2]
Bleeding[3]	0 (0)	2 (50)	0.2[2]
AKI	0 (0)	0 (0)	-
Urosepsis	1 (50)	0 (0)	0.1[2]
BNC	0 (0)	0 (0)	-
Urinary incontinence	-	1 (25)	-
Change in Cr (mg/dL), mean ± SD	0.15 ± 0.4	-0.3 ± 0.3	0.4[1]
Change in Hb (g/dL), mean ± SD	3.9 ± 0.8	5.1 ± 1.7	0.5[1]
Hospital (d), mean ± SD	4.0 ± 1.4	4.8 ± 1.5	0.6[1]
Multiple procedures	0	3 (75)	0.08[2]
Avg. # stone procedures, mean ± SD	1.0 (0.0)	2.0 (0.8)	0.2[1]
Stone free	2 (100)	1 (25)	0.08[2]
Stone size (mm), mean ± SD	12.5 ± 6.4	10.4 ± 1.3	1.0[1]

[1]Wilcoxon Rank Sum; [2]Fisher's Exact; [3]Occurred at the time of prostatectomy. BNC: Bladder neck contracture; AKI: Acute kidney injury; Cr: Creatinine; Hb: Hemoglobin.

treatment approach. As such, given its low rate of complications, and need for secondary procedures, we conclude that there is a potential role for the simultaneous use of URS to treat symptomatic distal ureteral stones at the time of RP.

With a high incidence of prostate cancer[7-9] and urolithiasis in the aging male population[2], a significant proportion of these men may present with urinary stone disease discovered during cancer staging and treatment. In general, asymptomatic urolithiasis has an 8% prevalence with approximately 20% developing a symptomatic stone event within 1.3 years[16]; and, up to 26% may require surgical intervention[18]. However, the appropriate management of the asymptomatic patient that is incidentally found to have stone disease prior to radical prostatectomy remains unknown. Furthermore, for the symptomatic patient that presents a trial of passage may be a reasonable option. However, in those patients who fail medical expulsion therapy[25,26], elect for surgical management[27], or have high-risk prostate cancer the timing of urinary stone treatment becomes paramount.

Meanwhile, the risk of injury to the vesicourethral anastomosis with instrumentation is likely greatest in the immediate postoperative period. Unfortunately, little work has been done to assess the true risk to radical prostatectomy patients undergoing instrumentation for urinary stone treatment in the perioperative period. Gibbons *et al*[28] evaluated the feasibility of retrograde endoscopy in the post-prostatectomy patient. They observed no complications or adverse effect on urinary continence in 21 patients with a mean interval between radical prostatectomy and retrograde endoscopy of 24 mo[28]. Although reassuring, their series may not reflect the true long-term risk due to a short follow-up and significant time between prostatectomy and endoscopy. Herein, we found no significant difference between groups with 14% developing bladder neck contracture and 39% having mild to moderate urinary incontinence at last follow-up. Currently, depending on method of evaluation, 60%-93% of patients will regain urinary continence by 12 mo[20] and 2%-18% develop bladder neck contracture[22], which is not considerably different from our cohort.

In our series complications occurred in 42% *vs* 30% and additional stone procedures in 33% *vs* 10% of staged and simultaneous patients, respectively. We included complications secondary to the stone procedure (urosepsis and steinstrasse) and radical prostatectomy (bleeding). Thus, our increased rate of overall complications is not typically observed with traditional stone procedures. Furthermore, after subgroup analysis of patients undergoing URS and SWL, there remained no significant difference in outcomes. However, in SWL, 50% of staged patients developed steinstrasse and 75% required subsequent procedures which may place a patient at undue risk following prostatectomy. Salem *et al*[29] prospectively evaluated over 3000 patients undergoing SWL and noted a retreatment rate of 37% and steinstrasse in 24% of patients. Our increased retreatment rate reflects an attempt to render all patients stone-free following SWL and limit acute stone events following radical prostatectomy. As such, given the high rate of secondary procedures we feel that SWL should only be performed in a staged setting.

Multiple studies have established the importance of stone size, location and number in predicting stone-free rates[30-35]. Rippel *et al*[30] evaluated patients with CT imaging 30 to 90 d post-operatively. On univariate analysis 49% patients with multiple and 50% with intrarenal calculi had residual stone fragments greater than 2 mm. In our study, only stone location was significantly associated with a risk of retreatment as 38% of patients with proxi-

mal or multiple stones required additional procedures. Meanwhile our stone-free rate, although not significantly different between simultaneous and staged patients, was lower in patients with multiple or upper tract stones (P = 0.02) with no difference based on stone burden (P = 0.3).

Interestingly, patient symptomology was significantly associated with an increased risk of subsequent procedures as 60% of asymptomatic patients required additional stone treatment. We hypothesize that urinary obstruction over time allows for passive dilation of the collecting system thus increasing compliance and allowing ease of stone passage and instrumentation. Frequently, in our experience, the treatment of asymptomatic patients in a single-stage setting can be difficult often requiring multiple procedures and leading to increased complications. Keeley *et al*[36] prospectively evaluated patients undergoing SWL treatment of small (< 15 mm) asymptomatic renal calculi and found a stone-free rate of only 28% at 2.2 years. Despite evidence suggesting that a patient's symptomatology may be a predictor of treatment outcomes; this question has yet to be previously addressed among patients undergoing URS.

Certain limitations of our study exist. We acknowledge that the small patient population, and its retrospective nature, may limit any definitive clinical recommendations for a change of practice. Furthermore, we do not know the incidence of symptomatic progression of urinary stone disease following RP in those men who undergo expectant management preoperatively. Despite these limitations, this study attempts to address the safety, feasibility and utility of performing simultaneous stone treatment at the time of radical prostatectomy. We demonstrate no difference in outcomes which may suggest a role for simultaneous stone removal, specifically URS, in appropriately selected patients. Further prospective trials are needed to identify eligible patients, risk factors for significant short and long-term complications and cost-analysis of a single-stage procedure.

The current study demonstrates that simultaneous treatment of symptomatic distal urolithiasis with URS at the time of radical prostatectomy is safe and efficacious. Meanwhile, given the high rate of residual stone fragments and re-instrumentation following SWL, we recommend it be performed in a staged fashion. Finally, in asymptomatic patients, or those with multiple or upper tract stones, one should consider a staged approach due to the increased risk of additional procedures and reduced stone-free rates.

COMMENTS

Background

The prevalence of urinary stone disease in the male population ages 50 to 74 years old has increased from 13% from 1988-1994 to 19% in 2007-2010, representing a roughly equivalent to 40% relative increase in stone disease. A similar increase in the incidence of prostate cancer has also been observed due to PSA screening. As such, a significant number of male patients diagnosed with prostate cancer may harbor urolithiasis. If urinary stone disease is discovered, these patients pose a complex management dilemma given that 44% of asymptomatic patients with urolithiasis will develop symptoms within 1.3 years. An acute stone event within the immediate post radical prostatectomy period poses a unique concern; specifically, instrumentation of the fresh vesicourethral anastomosis has the potential for anastomotic injury with resultant long-term urinary incontinence and/or bladder neck contracture.

Research frontiers

Ongoing research in the field of urinary stone disease is attempting to identify modifiable patient risk factors to prevent future stone events. Moreover, among men undergoing radical prostatectomy for prostate cancer, significant research efforts are ongoing, including investigation of minimally invasive techniques and minimizing post prostatectomy complications such as urinary incontinence and bladder neck contracture; which can be disabling.

Innovations and breakthroughs

To the best of our knowledge, this is the first study to investigate the safety and efficacy of synchronous upper tract urinary stone treatment at the time of radical prostatectomy. One previous study has evaluated the association between upper tract endoscopy following radical prostatectomy and stress urinary incontinence. They found no difference in outcomes among men underwent ureteroscopy at a mean 24 mo following prostatectomy.

Applications

With a high incidence of prostate cancer and urolithiasis in the aging male population, a significant proportion of these men may present with urinary stone disease discovered during cancer staging and treatment. In general, asymptomatic urolithiasis has an 8% prevalence with approximately 20% developing a symptomatic stone event within 1.3 years; and, up to 26% requiring surgical intervention. Meanwhile, the risk of injury to the vesicourethral anastomosis with instrumentation in the setting of an acute stone event is likely greatest in the immediate postoperative period. As such, the appropriate management and timing of treatment in these men is of paramount significance. The potential advantages of a synchronous approach include the minimization of perioperative complications associated with urolithiasis and the need for additional procedures. The current study demonstrates that simultaneous treatment of symptomatic distal urolithiasis with ureteroscopy at the time of radical prostatectomy is safe and efficacious. Meanwhile, we noted a high rate of residual stone fragments and re-instrumentation following shock wave lithotripsy and as such recommend it be performed in a staged fashion. Finally, in asymptomatic patients, or those with multiple or upper tract stones, one should consider a staged approach due to the increased risk of additional procedures and reduced stone-free rates.

Terminology

Radical prostatectomy is the surgical removal of the prostate gland for the treatment of prostate cancer. Ureteroscopy is a minimally invasive endoscopic procedure to diagnose and treat upper urinary tract disorders. Shock Wave Lithotripsy is a technique for fragmenting a kidney stone with a shock wave that is produced outside the body. Steinstrasse is a complication of shock wave lithotripsy for urinary tract calculi in which stone fragments obstruct the renal unit. Percutaneous Nephrolithotomy is a technique for treating upper tract urinary stone disease by which percutaneous access into the renal unit is obtain. Stone Free refers to no residual stone fragments following stone treatment.

Peer review

The present study by Amy E Krambeck is investigated the differences in perioperative and long-term outcomes of patients, which treated for urolithiasis at the time of radical prostatectomy (simultaneous) in the preoperative period (staged). The results showed that the simultaneous ureteroscopic treatment of symptomatic urolithiasis appeared to be safe and efficacious with radical prostatectomy. In general, the work was interesting, except several issues to be addressed to increase the quality of the present work.

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RETROSPECTIVE STUDY

Adjuvant chemotherapy and acute toxicity in hypofractionated radiotherapy for early breast cancer

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Abstract

AIM: To evaluate the effect of chemotherapy to the acute toxicity of a hypofractionated radiotherapy (HFRT) schedule for breast cancer.

METHODS: We retrospectively analyzed 116 breast cancer patients with T1, 2N0Mx. The patients received 3-D conformal radiotherapy with a total physical dose of 50.54 Gy or 53.2 Gy in 19 or 20 fractions according to stage, over 23-24 d. The last three to four fractions were delivered as a sequential tumor boost. All patients were monitored for acute skin toxicity according to the European Organization for Research and Treatment of Cancer/Radiation Therapy Oncology Group criteria. The maximum monitored value was taken as the final grading score. Multivariate analysis was performed for the contribution of age, chemotherapy and 19 *vs* 20 fractions to the radiation acute skin toxicity.

RESULTS: The acute radiation induced skin toxicity was as following: grade Ⅰ 27.6%, grade Ⅱ 7.8% and grade Ⅲ 2.6%. No significant correlation was noted between toxicity grading and chemotherapy (P = 0.154, χ^2 test). The mean values of acute toxicity score in terms of chemotherapy or not, were 0.64 and 0.46 respectively (P = 0.109, Mann Whitney test). No significant correlation was also noted between acute skin toxicity and radiotherapy fractions (P = 0.47, χ^2 test). According to univariate analysis, only chemotherapy contributed significantly to the development of acute skin toxicity but with a critical value of P = 0.05. However, in multivariate analysis, chemotherapy lost its statistical significance. None of the patients during the 2-years of follow-up presented any locoregional relapse.

CONCLUSION: There is no clear evidence that chemotherapy has an impact to acute skin toxicity after an HFRT schedule. A randomized trial is needed for definite conclusions.

Key words: Hypofractionated radiotherapy; Breast can-

cer; Acute toxicity; Chemotherapy; Retrospective analysis

Core tip: The adjuvant radiotherapy for early breast cancer after lumpectomy is an established treatment. Hypofractionation is an attractive approach and the trend nowadays towards new techniques involving hypofractionation is huge, mainly due to the long waiting lists, patients' desire for fast treatment, better planning of radiotherapy with computed tomography-based target definition and better dose homogeneity assured by 3D conformal planning. The aim of the current study is to evaluate the potential effect of previous chemotherapy to the acute skin toxicity and the local control followed for 2 years in patients with breast cancer, treated with hypofractionated radiotherapy regimen.

Kouloulias V, Zygogianni A, Kypraiou E, Georgakopoulos J, Thrapsanioti Z, Beli I, Mosa E, Psyrri A, Antypas C, Armbilia C, Tolia M, Platoni K, Papadimitriou C, Arkadopoulos N, Gennatas C, Zografos G, Kyrgias G, Dilvoi M, Patatoucas G, Kelekis N, Kouvaris J. Adjuvant chemotherapy and acute toxicity in hypofractionated radiotherapy for early breast cancer. *World J Clin Cases* 2014; 2(11): 705-710 Available from: URL: http://www.wjgnet.com/2307-8960/full/v2/i11/705.htm DOI: http://dx.doi.org/10.12998/wjcc.v2.i11.705

INTRODUCTION

The adjuvant radiotherapy (RT) for early breast cancer after lumpectomy is an established treatment. The most widely used schedule for whole breast irradiation is 50 Gy in 25 fractions (conventional), while randomized trials comparing conventional radiotherapy schedules to different hypofractionation, have shown equivalent results[1]. A lot of shorter (accelerated hypofractionated) RT schedules have been already used in clinical practice[2-6]. Hypofractionation is an attractive approach and the trend nowadays towards new techniques involving hypofractionation is huge, mainly due to the long waiting lists, patients' desire for fast treatment, better planning of radiotherapy with computed tomography (CT)-based target definition and better dose homogeneity assured by 3D conformal planning.

However it is quite difficult to compare the treatment outcome due to the variation of clinical parameters, such as patient selection, chemo/hormonotherapy, differences in breast size, radiation dosimetry and RT techniques[2-6].

The aim of the current paper is to evaluate the potential effect of previous chemotherapy to the acute skin toxicity and to the local control followed for 2 years in breast cancer patients irradiated with this hypofractionated regimen.

MATERIALS AND METHODS

One hundred sixteen patients were retrospectively selected, between May 2004 and December 2010. Patients characteristics are shown in details in Table 1. All patients received radiotherapy with a total prescription dose of 50.54 Gy or 53.2 Gy by 2.66 Gy per fraction, in 19 or 20 fractions, over 23-24 d. The decision of giving either 19 or 20 fractions was made in terms of stage (T1, 2) or in case maxima in dose distributions more than 108%. The last three to four fractions were delivered as a sequential tumor boost. The patients were irradiated either at the Radiotherapy unit of the 1st Department of Radiology in ATTIKON University Hospital or at the Radiotherapy Unit of the 2nd Department of Radiology in Aretaieion University Hospital[7,8]. However, the follow-up was realized in several departments either in Athens or Larisa.

Table 1 Patients' characteristics

Age median (range)	58.5 (35-86)
T1	81
T2	35
Chemotherapy	
Yes	83
No	33

Inclusion criteria in this study were breast cancer patients with stage Ⅰ-Ⅱ invasive carcinoma after conservative surgery and axillary lymph node dissection. Any adjuvant chemotherapy had to be completed before the start of RT.

The exclusion criteria were: mastectomy, presence of Paget's disease, presence of autoimmune conditions, previous thoracic neoplasia (cancer, sarcoma, lymphoma), previous breast cancer operated with bad cosmesis, diagnosis of previous or concomitant malignancies or skin disease, breast size in craniocaudal dimension more than 20 cm (or alternatively less than 2500 mL) and presence of psychiatric or addictive disorders[7].

All patients were monitored for acute skin toxicity according to the European Organization for Research and Treatment of Cancer/Radiation Therapy Oncology Group (EORTC/RTOG) criteria, during radiotherapy schedule once per week and one month thereafter[9]. The maximum monitored value was taken as the final grading score. The primary outcome measure was radiation induced acute skin toxicity. The secondary end point was the local recurrence free survival. Clinical and laboratory tests suggested recurrent disease were investigated, while the criterion for local disease recurrence was recurrent tumor within the treated irradiated field. Hormonal therapy, if prescribed according to indications, was administered after the completion of radiotherapy.

Simulation and treatment planning

Patients underwent standard CT simulation in the supine position. The ipsilateral breast and tumor bed with surgical clips were contoured for the delineation of Clinical Target Volumes (CTV), while contralateral breast, left and right lung and heart were contoured as organs at risk (OARs)[10]. When surgical clips were not present, preoperative mammography and ultrasound data were used for

Table 2 Incidence of acute skin toxicity in terms of previous chemotherapy or not

		EORTC/RTOG radiation induced acute skin toxicity grade				Total
		0	1	2	3	
Chemotherapy	No	56/83 (67.5%)	18/83 (21.7%)	7/83 (8.4%)	2/83 (2.4%)	83
	Yes	16/33 (48.5%)	14/33 (42.4%)	2/33 (6.0%)	1/33 (3.0%)	33
Total		72/116 (62.1%)	32/116 (27.6%)	9/116 (7.8%)	3/116 (2.6%)	116

No significant correlation was noted (Pearson χ^2 P = 0.15). EORTC/RTOG: Organization for Research and Treatment of Cancer/Radiation Therapy.

tumor bed definition. The planning target volume of the tumor bed (PTV_t) was a 1-2 cm expansion around the clinical target volume (CTV). The ipsilateral breast volume was the planning target volume (PTV_B), excluding the chest wall and 0.5 cm from the skin[10].

Radiobiological issue

We used linear-quadratic (LQ) model in order to assess the equivalent of hypofractionation schedules to the Normalised Total Dose (NTD) if delivered in conventional scheme of 2 Gy per fraction[11-16]:

$NTD = D_{new}[(d_{new} + \alpha/\beta)/(2 + \alpha/\beta)]$

where Dnew and dnew are the total dose and dose per fraction for the hypofractionated schedule, respectively. Normalized Total Dose - NTD has been calculated and tabulated for both breast (α/β = 4 Gy) and acute reacting tissues (α/β = 10 Gy)[11-16]. When considering that α/β = 4, the NTD was 56.10 Gy and 59.05 Gy for 19 and 20 fractions, respectively. When considering that α/β = 10, the NTD was 53.3 Gy and 56.13 Gy for 19 and 20 fractions, respectively.

We used the QUANTEC trial for the dose constrains, as described below, concerning NTD values for an α/β = 3 (late reacting tissues)[17,18]: (1) Ipsilateral lung: < 15% of lung should receive less than 30% of prescribed dose; (2) Heart (left sided breast): Volume of heart getting 5% of dose (V5) should be less than 40%; (3) Heart (right sided breast): < 5% of heart should receive less than 5% of the prescribed dose; (4) Contralateral breast: should receive less than < 3% of prescribed dose to any point; and (5) Contralateral lung: < 15% of lung should receive less than 5% of prescribed dose.

Systemic therapy

Patients with axillary nodal metastases received adjuvant systemic treatment. Concerning the premenopausal women, two schedules were used: 62 patients received 4 cycles of epirubicin and endoxan every 2 wk, 3 wk brake and then 4 cycles taxotere every 3 wk; 54 patients received 6 cycles of cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) chemotherapy *iv* every 21 d. Postmenopausal patients received also tamoxifen 20 mg daily for 5 years, after the completion of radiotherapy. All patients received irradiation in a time post chemotherapy ranged 25-45 d.

Statistical analysis

The comparison of mean value of toxicity score between patients undergone adjuvant chemotherapy *vs* no chemotherapy was done with the Mann Whitney non-parametric test. The correlation of the incidence of toxicity grading with either the administration of chemotherapy or the prescribed schedule of 19 *vs* 20 radiotherapy fractions was performed with the χ^2 test. The impact of age, chemotherapy and total dose to the radiation induced acute skin toxicity was performed with the logistic linear regression analysis in two steps: first all variables were entered in the equation as a univariate analysis; second only variables with a statistical significance were entered in a multivariate model. The significance level was set at 0.05. All the analysis was performed using the SPSS ver. 10 software (IL, United States).

RESULTS

Thirty three patients underwent a radiotherapy schedule of 19 fractions while 83 underwent schedule of 20 fractions. Overall, acute radiation induced skin toxicity, according to European Organization for Research and Treatment of Cancer/Radiation Therapy Oncology Group criteria, was as following: grade Ⅰ 27.6%, grade Ⅱ 7.8% and grade Ⅲ 2.6%. The acute radiation induced toxicity score in details is shown in Table 2. No treatment interruption was occurred since no skin toxicity more than grade 3 was noted. No significant correlation was noted between toxicity grading and chemotherapy (P = 0.154, χ^2 test). The mean values of acute toxicity score in terms of chemotherapy or not, were 0.64 and 0.46 respectively (Figure 1). No significant difference was noted (P = 109, Mann Whitney test). No significant correlation was also noted between acute skin toxicity and radiotherapy fractions (P = 0.47, χ^2 test). The logistic regression analysis performed in two steps is shown in Table 3. According to univariate analysis, only chemotherapy contributed significantly to the development of acute skin toxicity but with a critical value of 0.05. However, in multivariate analysis chemotherapy lost its statistical significance.

None of the patients during the 2-years of follow-up presented with any locoregional relapse. The acute radiation skin toxicity decreased rapidly after the completion of radiotherapy. Three months post irradiation, 107 out of 116 (92.2%) patients presented grade 0 of skin toxicity, while 9 out of 116 (7.7%) presented only grade I acute skin toxicity.

DISCUSSION

The linear quadratic (LQ) is a well established model that

Table 3 Logistic regression analysis performed for analyzing the contribution of age, chemotherapy and radiotherapy fractions (19 *vs* 20) to the development of acute radiation induced skin toxicity

	Univariate analysis			Multivariate analysis		
	P	RR	95%CI	*P*	RR	95%CI
Age	0.31	-	-	0.41	-	-
Chemotherapy	0.05	2.35	1.01-5.52	0.057	-	-
19 *vs* 20 fractions	0.55	-	-	0.66	-	-

The univariate model chi-square with 3 degrees of freedom was 4.97 ($P = 0.17$). None of the variables entered to the multivariate model. RR: Risk ratio.

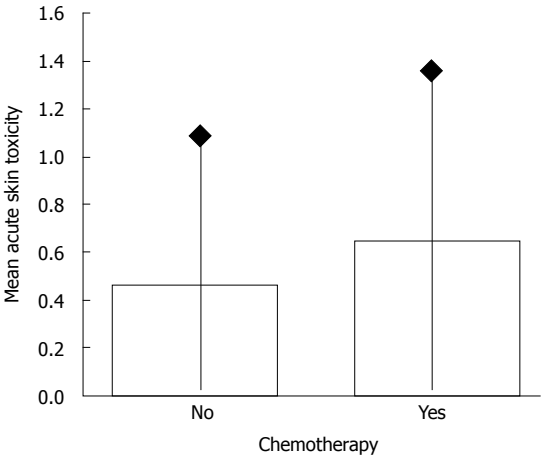

Figure 1 Mean acute skin toxicity score for patients undergone chemotherapy or not (*P* = 0.109, Mann Whitney test).

provides assessments of equivalent doses to both tumor and normal tissues[11-17].

Biological factors related to proliferation (overall time and delayed after irradiation), and the effect of dose per fraction, are basic knowledge necessary for the planning of new irradiation schedules which are effective in practice[11-16].

In our institution we have already reported on the efficacy of the certain hypofractionated schedule for breast cancer[7,8]. Moreover we have made a thorough dosimetric analysis for the dose deposited at the contralateral breast[19]. However, this is the first study according to our knowledge, evaluating the impact of adjuvant chemotherapy to the skin toxicity for a hypofractionated irradiation schedule for breast cancer. In univariate analysis the parameter of chemotherapy seems to have a significant impact to the radiation induced skin toxicity with a critical value of 0.05. However, in multivariate analysis chemotherapy lost its statistical significance. Thus eventually neither chemotherapy, nor the age and the total dose seemed to have any impact to acute skin toxicity.

Sanguineti *et al*[20] investigated whether chemotherapy administered at earlier or concomitant with radiotherapy, has an impact either to the RT duration or to the hematological profile. The RT schedule was consisted of 50 Gy in five weeks. The investigators concluded that there is no correlation in terms of toxicity between chemotherapy dose-density and dose-intensity of RT. However, the concomitant administration of chemotherapy and RT decreases the ability of prescribing a full irradiation scheme. The only toxicity observed was in white blood cells (WBC). The toxicity on late responding tissues with the combination of hypofractionation and chemotherapy was not investigated. In terms of multivariate analysis, no significant correlation was assessed between skin toxicity and weekly dose rate, while the analysis of potential factors associated with skin toxicity was not a subject of this study[20].

According to current literature concerning clinical guidelines and randomized trails, Hypofractionated RT in breast cancer patients offers equivalent outcome to the standard conventional schedule, in terms of tumor control and normal tissue damage[21-24]. In clinical practice the most commonly used schedule of 2.66 Gy in 16 fractions is equivalent to 50 in 2.0 Gy fractions, when the a/β value is equal to 3Gy. Any potential loss of therapeutic ratio (2.9 Gy loss of anti-tumor dose) would be compensating with the shorted treatment time due to reduced tumor repopulation and either adjuvant or neo-adjuvant chemotherapy[21].

One of the trials, published in 2002 by Whelan *et al*[23], compared a schedule of of 42.5 Gy in 16 fractions over 22 d (accelerated arm 266 Gy/fraction) with conventional breast irradiation consisted of 50 Gy in 25 fractions over 35 d (2 Gy/fraction). No boost was added. The randomized women had invasive breast cancer, free resection margins, uninvolved axillary lymph nodes. After 69 mo (more than 5 years) follow up the randomized trial determined that the accelerated arm was as effective as the conventional arm concerning the two outcomes- local control and cosmetic results. As it was obvious in the long term results, published in 2010, the local recurrence rate at 10 years was 7.5% in the conventional group as compared with 7.4% in the accelerated group[24]. The survival rate at 10 years was equivalent in both arms by means of 84.4% in the conventional group *vs* 84.6% in the accelerated group, while cosmetic outcomes were also similar concerning a rate of 4% or less grade 3 radiation induced toxicity[24].

The 5 year results of two big randomized trials - the United Kingdom Standardisation of Breast Radiotherapy (START) Trial A and START Trial B have been also reported[25,26]. START Trial A[25] compared each of two schedules of hypofractionation 41.6 Gy or 39 Gy in 13 fractions of 3.2 Gy or 3.0 Gy over 5 wk with conven-

tional whole-breast irradiation and START Trial B[26] compared 40 Gy in 15 fractions of 2.67 Gy over 3 wk with conventional irradiation 50 Gy in 25 fractions of 2 Gy. The interpretations of the results from the two trials were that the hypofractionation schedules offered similar rates of tumour control and normal tissue damage as the international standard fractionation schedule of 50 Gy in 25 fractions. The endpoints of both studies at term of tumor relapse, late normal tissue effects, and quality of life were at least as favorable as the standard schedule. Boost irradiation was according to protocol guidelines in both START trials, while adjuvant chemotherapy was used more widely than in Whelan et all trial[23], while up to nowadays follow-up, no significant increase in toxicity has been reported. Zygogianni *et al*[8] in a previous study, at the end of RT reported 24.1% of grade I and 9.3% of grade II acute skin toxicity, while 66.7% of the patients showed no radiation induced skin morbidity. In this study the results are equivalent with 27.6% and 7.8% of grade I and II skin toxicity, respectively.

Dorn *et al*[27] studied the skin toxicity in large breasts by an hypofractionated schedule of 42.56 Gy in 2.66 Gy per fraction. Of the 80 treated patients with large breasts, the maximum acute skin toxicity was mild erythema or hyperpigmentation in 70.0%, dry desquamation in 21.25% and focal moist desquamation in 8.75%. Maximum acute toxicity occurred after the completion of radiation in 31.9% of patients. Breast volume was the only patient-related factor significantly associated with moist desquamation on multivariable analysis ($P = 0.01$). Patients with breast volume > 2500 mL showed focal moist desquamation in 27.2% of cases *vs* 6.34% in patients with breast volume < 2500 mL ($P = 0.03$). In our case, according to eligibility criteria, all patients had a breast volume less than 2500 mL.

In another study referring to 44 patients with primary stage breast cancer after adjuvant chemotherapy and hypofractionated RT, Zygogianni *et al*[28] reported a significantly acute skin toxicity when the intermediate time between chemotherapy and RT was less than 20 d ($P < 0.05$). All patients in this study received irradiation 25 d at the minimum after chemotherapy.

Although, all the above mentioned trials studied skin toxicity according to the hypofractionated schedule, none of them explored the impact of chemotherapy on acute skin morbidity. According to our results, the hypofractioned radiotherapy for breast cancer is safe in terms of mild toxicity, independently with the sequential chemotherapy, if administered. Our acute toxicity is in accordance with the reported values in all previous published studies. Obviously, the maximum grade of skin toxicity was noted during the whole breast irradiation and not during the boost radiotherapy. On the other hand, it seems that chemotherapy might not be a major factor affecting the radiation induced morbidity. However, due to the retrospective nature of our study, it is difficult to extract safe conclusions, while a randomized prospective study is needed to answer the question: has chemotherapy a definite impact to radiation induced morbidity if a hypofractionated schedule is used? Consequently, the question is still open.

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COMMENTS

Background

The Hypofractionated irradiation for breast cancer patients has been involved in the routine clinical practice for several years. However, the impact of previous chemotherapy to radiation induced toxicity has not been studied thoroughly.

Research frontiers

No clear evidence that chemotherapy has an impact to radiation induced skin toxicity has been noted.

Innovations and breakthroughs

This is a retrospective study documenting the absence of clear impact of previous chemotherapy to Hypofractionated radiotherapy for breast cancer.

Applications

Clinicians that decide to use hypofractionated irradiation for breast cancer may prescribe this schedule independently to previous chemotherapy.

Terminology

Hypofractionated: irradiation schedule with more than 200 cGy per fraction.

Peer review

In this study, the authors evaluated the impact of chemotherapy to the acute toxicity of a hypofractionated irradiation schedule for breast cancer. Delivering postoperative radiotherapy in a shorter time could effectively be much more convenient for patients and several clinical randomized trials have shown that hypofractionated adjuvant radiotherapy in breast cancer offers similar rates of tumour control and normal tissue damage as the standard schedule.

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CASE REPORT

Concomitant achondroplasia and Chiari Ⅱ malformation: A double-hit at the cervicomedullary junction

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Abstract

We report the first case of a neonate with concurrent Chiari Ⅱ malformation and achondroplasia. Although rare, both these conditions contribute to several deleterious anatomical changes at the cervicomedullary junction and thus predispose to acute hydrocephalus. Although our patient was initially asymptomatic, hydrocephalus ensued several weeks after birth and required cerebral spinal fluid diversion. We discuss the potential links between the two conditions, the pathophysiology, and the important clinical implications for the management of the increased risk of hydrocephalus.

Key words: Achondroplasia; Chiari Ⅱ malformation; Hydrocephalus; Shunt failure; Cervicomedullary junction; Cerebral spinal fluid diversion

Core tip: Achondroplasia and Chiari Ⅱ malformations can induce similar anatomical changes at the cervicomedullary junction which increase the risk of acute hydrocephalus. Chiari decompression may not always be necessary, however, diligent and acute follow-up is important to monitor for signs of impeding hydrocephalus. If cerebral spinal fluid diversion is required, remember that shunt failure is common in the pediatric age group and also requires close follow-up.

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INTRODUCTION

Achondroplasia is the most common cause of dwarfism, occurring at a frequency of 1 and 26000 live births[1]. Mutations of the *FGFR3* gene, which encodes a tyrosine kinase receptor that is deferentially expressed during various stages of development, are responsible for the characteristic short-stature and macrocephaly[2,3]. The condition follows an autosomal dominant inheritance pattern with complete penetrance, however 80%-90% of cases are due to sporadic mutation[1,4]. The FGFR3 gene has been mapped to chromosome 4p16.3, and is part of a larger family of fibroblast growth factor receptor genes which play important roles in skeletal development[2,3].

The Chiari Ⅱ malformation (CM Ⅱ) is a well characterized congenital malformation of the central nervous system. Although the exact mechanism is still disputed, the condition is defined by a small posterior fossa and caudal displacement of the brainstem and cerebellum through the foramen magnum[5]. In addition, all cases of CM Ⅱ are associated with a myelomeningocele[5] which can be further complicated by hydrocephalus, syringomyelia, heterotopias, and agenesis of the corpus callosum are only some of the commonly reported sequelae[5-7].

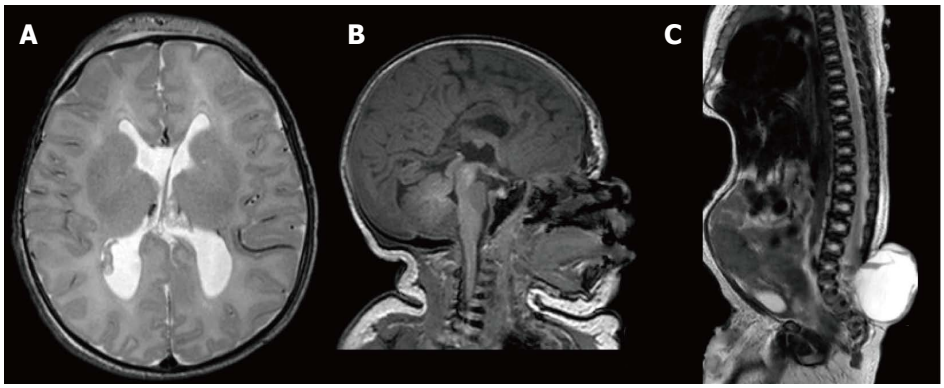

Figure 1 Pre-operative magnetic resonance imaging imaging of the patient to evaluate and screen for anatomical abnormalities. A: Axial T2 MRI of the head at birth demonstrating no signs of hydrocephalus; B: Sagittal T1 MRI of the head and neck at birth with evidence of a tight cervicomedullary junction, a small posterior fossa, and hypoplastic corpus callosum and cerebellar vermis; C: Sagittal T2 MRI of the spine at birth demonstrating a large 7 cm × 7 cm sacral myelomeningocele with evidence of tethering. MRI: Magnetic resonance imaging.

In our literature review we found two case reports of patients with both achondroplasia and Chiari I malformations[8,9], however to our knowledge there are no published case reports of concomitant achondroplasia and CM Ⅱ. Here we report the first such case in a neonate, and discuss the potential links between the two conditions, the pathophysiology, and the management of the increased risk of hydrocephalous.

CASE REPORT

History of present illness

A 1 d old male born after 39-3/7 wk of gestation to a 39-year-old gravid 1, para 0 women presented after delivery for surgical correction of a sacral mass. During pregnancy, an elevated AFP was noted and ultrasound findings demonstrated enlarged ventricles, large for gestational age status, and a sacral myelomeningocele. The infant was delivered *via* cesarean section with no complications; at birth, 1 and 5 min APGARs were 8 and 9 respectively. The child's cranium appeared relatively macrocephalic and measured in the 75th percentile with a short cranial base and mild frontal bossing. A 7 cm × 7 cm sacral myelomeningocele was noted and no cerebral spinal fluid (CSF) leak was evident. The extremities showed shortening of the femurs and humeri with relatively long fibulae and a trident confirmation of the hands. The patient had a short stature with an upper-lower segment ratio of 1.9 (normal 1.6 to 1.7), these exam findings initiated a genetic and skeletal survey for achondroplasia. The remainder of the physical and neurological exam were normal.

Imaging studies

An axial T-2 magnetic resonance image (MRI) of the head showed no signs of hydrocephalus (Figure 1A). There was no evidence of a tonsillar herniation, however, a tight cervicomedullary junction was noted on the sagittal T-1 MRI of the head (Figure 1B), and the lateral and third ventricles were slightly enlarged. The corpus callosum and cerebral vermis were noted to be hypoplastic and a small posterior fossa with frontal bossing were evident. A sagittal T-2 MRI of the spine (Figure 1C) demonstrated a well circumscribed hyperintense sacral mass protruding dorsally, with a loss of posterior spinal elements distal to L3. There was some evidence of cauda equina involvement and tethering of the cord.

Operative course

The patient's radiographic and physical exam findings were consistent with a CM Ⅱ. The patient was taken to the operating room on the same day of presentation to undergo repair of the myelomeningocele. A typical elliptical incision was made adjacent to the defect with midline extension caudal and rostral to the dome. The myelomeningocele was delicately dissected away from the dome skin and the surrounding fascial and dural layers. The termination of the placode was detethered from the dome skin, and the dorsal and ventral nerve roots were mobilized laterally. The lateral edges of the placode were approximated and sutured to form a closed cavity. The dura was then closed and no signs of CSF leak were evident after valsalva. Finally, the fascial layers and skin were re-approximated; some trimming of the excess skin was necessary. The operation was completed without complications and the patient's recovery was monitored in the neonatal intensive care unit.

Post-operative course

A genetic evaluation for achondroplasia was positive for a mutation of the *FGFR3* gene on chromosome 4 showed a glycine to arginine substation mutation at the 380th amino acid residue confirming a diagnosis of achondroplasia. It was not immediately clear if the CM Ⅱ was related to the patients' concomitant achondroplasia. The patient was monitored post-operatively for 6 d. During that period the fontanelles remained soft and there were no signs of increased intracranial pressure (ICP). The patients' family was counseled on the symptoms of hydrocephalous and the patient was discharged home with

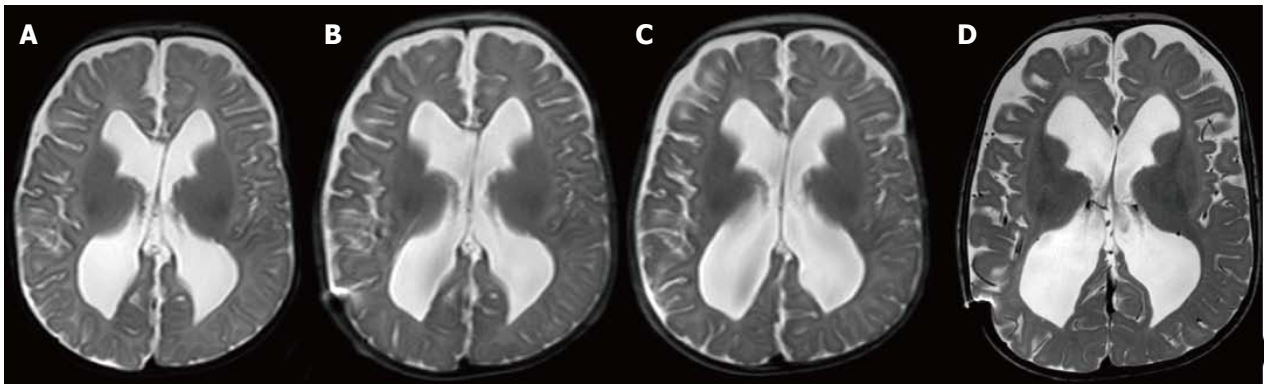

Figure 2 T-2 weighted magnetic resonance imaging demonstrating shunt failure and progression of hydrocephalous over the course of 4 mo of treatment. A: Pre-shunting axial T-2 weighted MRI ordered after patient had increased head circumference and suture splaying demonstrating ventriculomegaly; B, C: Subtle increase in ventricular size at 2 wk (B) and 6 wk post-shunting (C); D: At 4 mo post-operative shunting with significant increase in ventriculomegaly and extra axial fluid spacing. MRI: Magnetic resonance imaging.

instructions to follow up in 2 wk.

Progressive hydrocephalus

In the subsequent weeks, the patient had bi-weekly clinical and ultrasound exams which were normal. At 8 wk however, the patients head circumference was in the 97th percentile, the anterior fontanelle was full and pulsatile with signs of sagittal suture splaying, but the patient had no signs of respiratory distress. A T2 MRI (Figure 2A) showed evidence of ventriculomegaly with increased extra-axial spacing. Given the physical exam and radiographic findings we placed a ventriculoperitoneal (VP) shunt in the right lateral ventricle without incident.

After discharge the patient was monitored with serial MRIs (Figure 2B, C) which demonstrated subtle but continued ventriculomegaly. During this time the patient was asymptomatic and had normal exam findings.

Shunt failure

Four months following shunt placement, the patient was found to have an enlarged head circumference that measured above the 95th percentile. The patient was reported to be less active than usual and the anterior fontanelle was full but soft. A T-2 MRI demonstrated the VP shunt catheter was no longer in the lateral ventricle; subsequently, the lateral and third ventricle had enlarged (Figure 2D) and there was evidence of encroachment of the cerebellar tonsils into the spinal canal. The patient required shut revision, which was completed without complications. At the time of the shunt revision, somatosensory evoked potentials were within normal limits and Chiari decompression was not carried out.

The patient is now 10 mo old and we continue to monitor his head circumference which has stabilized since shunt revision.

DISCUSSION

Genetic associations

Embryogenesis is a complex physiologic phenomenon that is subject to a wide range of exogenous and endogenous forces that can have significant impact on developmental outcomes. At times, these changes are so gross they can be detected in-utero as in the case of a CM Ⅱ, in which a myelomeningocele is evident in pre-partum ultrasound. Conversely, in conditions like achondroplasia, developmental changes become apparent shortly after birth. Although the exact mechanism by which these effects take place are not entirely delineated, understanding them is crucial to the development of preventive and therapeutic strategies.

As in our case, almost all cases of achondroplasia are due to a substitution mutation of the 380th amino acid Gly for an Arg residue, which resides in the transmembrane domain of the receptor protein[2,3]. Gene expression studies in mice have shown elevated levels of mRNA encoding the FGFR3 protein in the rudimentary cartilage of all premature bone during organogenesis[10]. The effects of achondroplasia on the developing calvarium can produce signs and symptoms similar to those seen in CM Ⅱ. In addition to the characteristic macrocephalic changes commonly seen, changes in the shape and size of the foramen magnum, cervical stenosis, cervicomedullary compression and upward herniation of the brainstem are common[8,11].

Although there are several proposed hypotheses describing the pathogenesis of CM Ⅱ, the exact mechanism remains elusive. Animal models have demonstrated that open neural tube defects (NTD) are causative in the case of CM Ⅱ. NTD that were surgically created in mouse, rat, and sheep models replicate the hindbrain herniation through the foramen magnum that is stereotypical of CM Ⅱ[12-14]. This finding has two important implications; firstly it lends considerable evidence to the widely accepted "unified theory" of CM Ⅱ[6]. This theory alleges the loss of CSF through the open caudal NTD causes a subsequent drop in ICP. This loss of pressure at a critical point during fetal development results in poor cranial vault expansion culminating into a small posterior fossa. The unexpectedly narrowed posterior fossa leads

to the caudal displacement of the brainstem and cerebellum through the foramen magnum[6]. Secondly, the causal relationship of NTD and CM Ⅱ has valuable corollaries for prevention. Folic acid supplementation has been found to reduce the incidence of NTD by 70%[15]. The incidence of CM Ⅱ has not been well studied to determine whether the expected decrease exists following the increased use of folic acid supplementation.

Due to the association of folic acid and NTD, there has been considerable research evaluating the role of enzymes and transport proteins involved in its metabolism, namely MTRR, MTHFD1 and FOLR1-2[16]. However, these genes appear to have little relation to those of achondroplasia and make up only a small portion of candidate genes. The genetic causes of NTD appear to be far more complex and varied than originally anticipated; over 200 gene mutations in mice are known to cause NTD[17]. Similarly in humans, NTD defects arise in the setting of multiple syndromes (Pallister-Hall, Walker-Warburg and Fanconi anemia among others) and chromosomal abnormalities including Trisomies 13 and 18[18-20]. Of the wide range of potential gene candidates we focused on reports of mutations involving chromosome 4, where the *FGFR3* gene is located. In a small series of 5 autopsy reports of fetuses with Wolf-Hirschhorn syndrome due to partial mutations (deletion/substitution) of the short arm of chromosome 4, three patients had sacral dimples, while 2 had partial or complete agenesis of the corpus callosum, all patients exhibited growth retardation, and had consistent craniofacial abnormalities including frontal bossing[21]. Furthermore, reports of achondroplasia and other spinal dysraphisms exist including tethered cords and lipomas indicating the range of phenotypes that ensue from genetic mutations in this region[22,23].

Familial studies of Chiari malformations are limited mainly to Chiari I malformations, as such, the genetics of CM Ⅱ are not as well characterized. Animal models have suggested possible gene candidates. The Splotch mouse model for example can produce NTD and the hindbrain herniation characteristic of the CM Ⅱ[6]. The genetic mutation responsible for this phenotype in mouse models was mapped to the human *Pax*-3 gene on chromosome 1, encodes transcription factors which play various roles in embryogenesis[24,25]. Further studies in humans however, demonstrated that mutations in Pax-3 generate distinct features not commonly seen in CM Ⅱ, namely deafness and abnormal pigmentation which were later characterized into a distinct Waardenburg Syndrome[25,26].

Clinical management

Given our patients' concurrent conditions, the concern for hydrocephalus was high. Brainstem herniation as a result of hydrocephalus in both CM Ⅱ and achondroplasia can be acutely progressive, and greatly increases the risk of apneic spells and acute respiratory failure[1,11,27]. At the time of presentation we believed the degree of cervicomedullary constriction present did not warrant surgical Chiari decompression, as a result the patient underwent myelomeningocele repair with acute follow-up. Although our patient ultimately required CSF diversion, there were no overt signs of respiratory distress, spasticity, or dysphagia which would warrant a surgical Chiari decompression. In a large series of 148 patients with CM Ⅱ, only 14% of patients required surgical decompression[7]. Treating the obstructive hydrocephalus by shutting is a more common method that is associated with fewer risks. In a series of 71 cases of CM Ⅱ, 64 (90%) patients had hydrocephalus, 89% of which required VP shunting[28]. As in our case, shunt placement necessitates close follow-up and thorough patient education. Unfortunately, our patient experienced shunt failure due to tip migration, a risk associated with this treatment. A large series of 1015 patients who underwent VP shunting reported a failure rate of 46.3%, in the pediatric group however, failure rates were reported to be 79.2%, the majority of which occurred in the first 6 mo[29]. Importantly, in patients with spinal dysraphisms, as in our case, failure rates were 84.8%[29]. At last follow up (10 mo) the patient was symptom free with signs of improved CSF outflow. Due to the compounding effects of both underlying conditions on the potential hydrocephalus we continue to monitor the patient with routine monthly follow-up.

In conclusion, both achondroplasia and the CM Ⅱ are relatively common as independent conditions; however, they very rarely occur concomitantly. Importantly, the CM Ⅱ is a consequence of NTDs which appear to have multifocal genetic and environmental etiologies. Although the genes involved in achondroplasia appear to be distinct from those of the CM Ⅱ, due to the complexity of embryologic development, there may be key interactions between the downstream pathways which may account for some of the similar anatomic changes seen at the cervicomedullary junction. As such the management of the potential hydrocephalus that may arise within patients with this unique predisposition requires acute and diligent follow up and patient education.

COMMENTS

Case characteristics

A newborn boy presented with macrocephaly, short limbs, and a sacral mass.

Clinical diagnosis

Concurrent achondroplasia and Chiari Ⅱ malformation.

Differential diagnosis

Myelomeningocele has a unique gross presentation however a sacrococcygeal teratoma should be considered and the two conditions can be easily differentiated using magnetic resonance imaging. The differential of a newborn with macrocephaly is quite large and includes congenital infections, obstructive hydrocephalus, metabolic conditions (Canavan's disease, Alexander's disease, *etc.*), and osteogenesis imperfecta are only a few to consider.

Laboratory diagnosis

A genetic test indicated a missense mutation of the *FGFR3* gene on chromosome 4 confirming a diagnosis of Achondroplasia.

Imaging diagnosis

MRI of the head and spinal column confirmed a diagnosis of Chiari Ⅱ malformation.

Treatment

Surgical myelomeningocele repair and ventriculoperitoneal shunting due to

hydrocephalous is a standard treatment.

Related reports

This is the first reported case of both a Chiari Ⅱ malformation and achondroplasia in the same patient. Cases of concurrent Chiari I malformation and achondroplasia have been reported in references 7 and 8.

Term explanation

Spina bifida is an incomplete closure of the spine during embryogenesis. A myelomeningocele is a form of spina bidifia that includes a herniation of the spinal meninges through the spinal defect.

Experiences and lessons

Shunt failure is more common in pediatric patients with spinal dysraphisms, generally occurring within the first 6 mo.

Peer review

The manuscript of Awad *et al* describes a neonate case with concomitant achondroplasia and Chiari Ⅱ malformation. According to a literature review performed by the authors this is the first case report of a patient with this combination. This is definitely an interesting case that is thoroughly documented. Everything seems to be very well described.

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CASE REPORT

Bevacizumab maintenance in metastatic colorectal cancer: How long?

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Abstract

The management of patients with non-progressive metastatic colorectal cancer after six months of treatment has not yet been codified. The most relevant concerns are the effectiveness of maintenance *vs* discontinuation, and the tolerability of prolonged treatment. Here we report the case of a 72-year-old man affected by colorectal cancer with lung metastases who achieved a complete response after receiving capecitabine, oxaliplatin and bevacizumab for six months, and bevacizumab alone for six months. Bevacizumab was continued as maintenance regimen for more than three years. It was discontinued because of an arthroplasty. Fifty-eight months after beginning first-line treatment, the patient remains free from relapse. Adverse effects were minimal and easily controlled.

Key words: Metastatic colorectal cancer; Bevacizumab; Maintenance

Core tip: A colorectal cancer patient with lung metastases received bevacizumab combined with chemotherapy for six months, and then bevacizumab monotherapy as maintenance treatment for more than three years. The patient achieved a complete response without evidence of side effects. He remains relapse free 58 mo after diagnosis.

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INTRODUCTION

The management of metastatic colorectal cancer (mCRC) has evolved over the past decade[1]. Patients receiving irinotecan[2], oxaliplatin[3] and fluorouracil achieve the best outcome (median survival, approximately 21 mo), regardless of treatment sequence[4]. Adding biological drugs such as anti-vascular endothelial growth factor (VEGF) or anti-epidermal growth factor receptor (EGFR) monoclonal antibodies to chemotherapy improved survival further[5]. The anti-VEGF monoclonal antibody bevacizumab significantly prolonged survival when added to first-line[6] or second-line chemotherapy[7]. Recent clinical

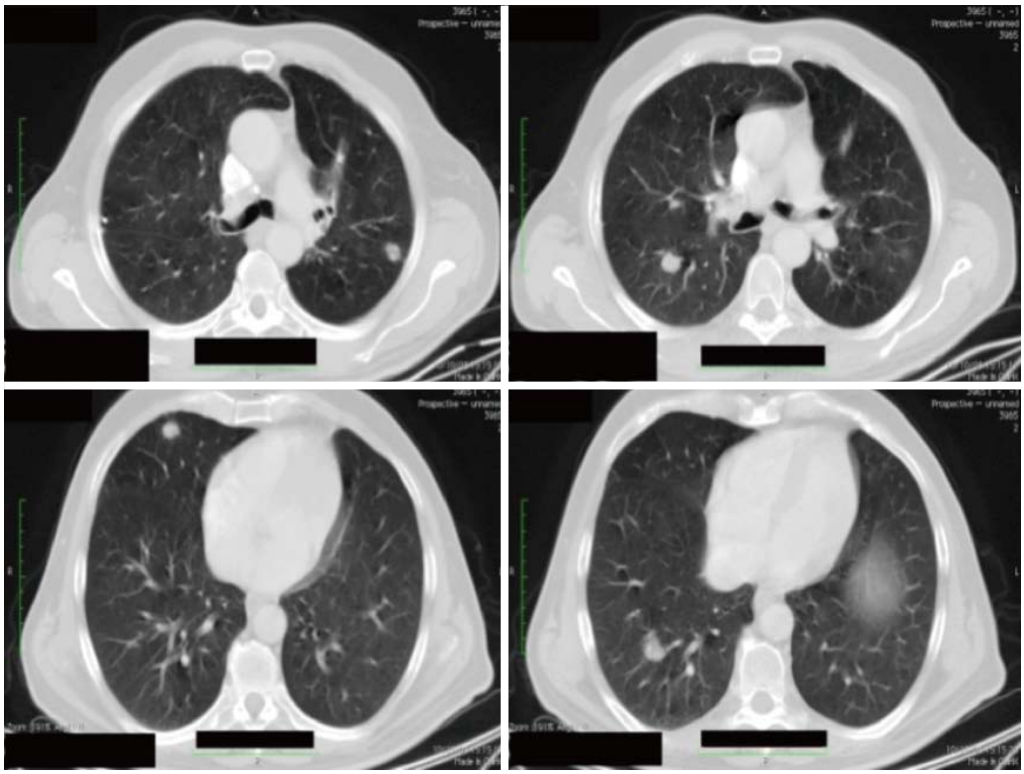

Figure 1 Thorax computed tomography-scan before starting chemotherapy (October 2008).

trials showed a clinical benefit in patients receiving bevacizumab even beyond progression[8,9].

Although often used in clinical practice, maintenance therapy in non-progressive patients after four-six months of chemotherapy ± biological drugs is not yet codified in terms of duration (indefinitely until disease progression?) and type of drugs (same chemotherapy regimen, simplified chemotherapy, targeted drug alone?). The most relevant concerns are the effectiveness of maintenance *vs* discontinuation, and the tolerability of such prolonged treatment.

Here, we report the case of a 72-year-old man affected by mCRC who obtained a complete response after treatment with capecitabine, oxaliplatin and bevacizumab for six months, followed by bevacizumab alone for a further six months. He then continued with bevacizumab as maintenance treatment for the following three years with no evidence of disease relapse or toxicity.

CASE REPORT

In October 2008, a 72-year-old man underwent left hemicolectomy for an obstructing mass located at the sigmoid-rectal junction. The pathological diagnosis was an undifferentiated (G3) adenocarcinoma, invading through the muscularis mucosae up to the peri-colic fat tissue (pT3); 12 nodes were isolated, all of which were metastatic (pN2). Radiological staging by contrast enhanced CT-scan showed several lung lesions (4 measurable) up to 20 mm in diameter (Figure 1). No liver metastases were detected. KRAS mutational status showed a mutation in codon 12 of exon 2.

The patient was referred to the Division of Medical Oncology of the University of Naples "Federico II" in November 2008 to begin first-line chemotherapy. He was in good condition (ECOG performance status = 1), and was only taking an ACE-inhibitor for arterial hypertension. Serum tumor markers exceeded the upper normal level: CA19.9 was 54 U/L (normal values < 37 U/L), and CEA 23.3 ng/mL (normal values < 5 ng/mL).

He began chemotherapy with the XELOX + bevacizumab schedule (capecitabine 1000 mg/m^2 twice daily, days 1-14; oxaliplatin 130 mg/m^2, and bevacizumab 7.5 mg/kg day 1, every 21 d). The work-up consisted of blood cell count and hematology before each cycle, and CT-scan every three months (or four cycles). Arterial blood pressure was measured before and after bevacizumab administration on day 1 and, thereafter, once daily with an electronic sphygmomanometer. The worse adverse events were: grade 1 peripheral neuropathy, grade 2 arterial hypertension, grade 1 hand-foot syndrome and grade 2 thrombocytopenia. Due to the worsening of arterial hypertension after the first treatment cycle, a diuretic and a calcium channel blocker were added to the antihypertensive treatment, which resulted in good blood pressure control. Bevacizumab administration remained unchanged, and blood pressure was well controlled.

Re-staging performed by whole-body CT scan after the fourth and the eighth (Figure 2) cycle of treatment showed a stable disease according to RECIST criteria. Thus, after completing eight courses (six months), capecitabine and oxaliplatin were discontinued and main-

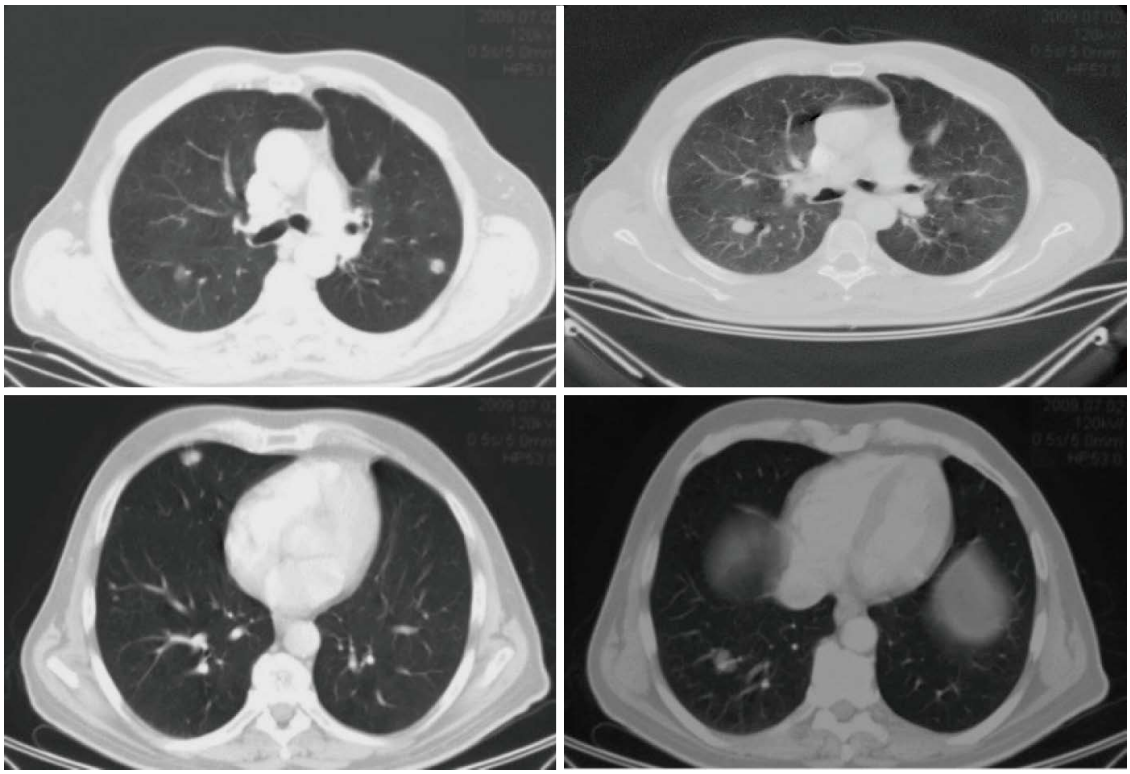

Figure 2 Thorax computed tomography-scan after 8 cycles of treatment. Note stabilization of the disease according to RECIST criteria (June 2009).

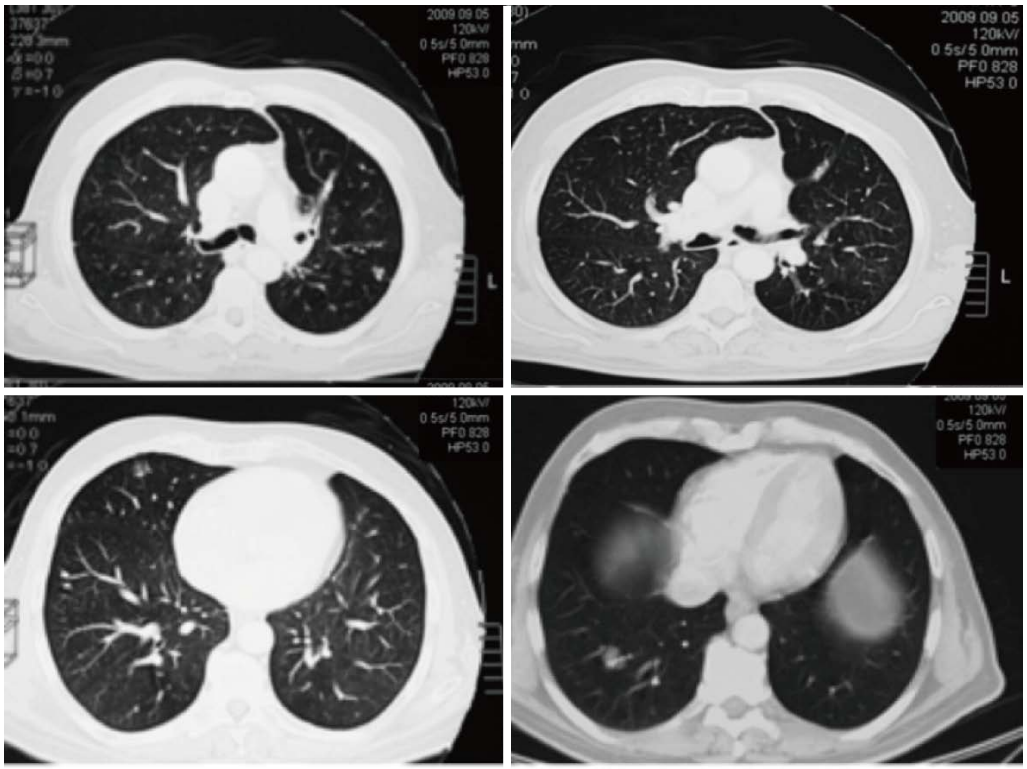

Figure 3 Thorax computed tomography-scan after two months of maintenance treatment. Note a partial regression of disease according to RECIST criteria (September 2009).

tenance with bevacizumab alone (7.5 mg/kg every 21 d) was started. During the maintenance period, re-staging by whole-body CT scan was scheduled every three months. In September 2009, the CT scan showed a significant reduction of the maximum diameter of the four measurable lung metastases (Figure 3), which were no longer

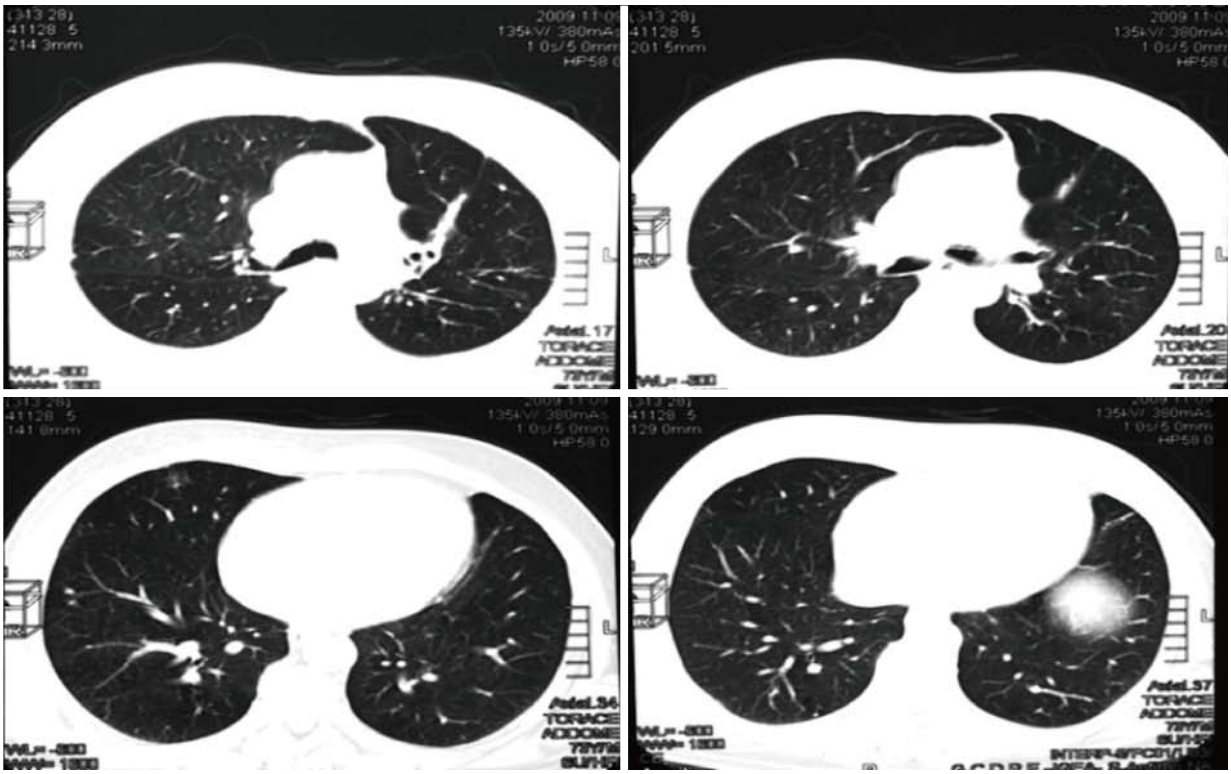

Figure 4 Thorax computed tomography-scan after 4 mo of maintenance treatment. The disease has completely regressed according to RECIST criteria (November 2009).

detected after a further 3 mo of treatment (November 2009) (Figure 4).

The patient continued with bevacizumab for the following 44 mo, remaining free from metastases (Figure 5), and without reporting any adverse event. Serum marker levels mirrored the outcome of the lung metastases throughout treatment and follow-up (Figure 6). In January 2013, bevacizumab was discontinued to enable the patient to undergo hip arthoplasty because of right coxarthrosis. Currently (June 2014), 68 mo after diagnosis, the patient has a good ECOG performance status with no evidence of metastatic disease (Figure 7). He attends follow-up controls every three months.

DISCUSSION

Here we report the case of a 72-year-old man with multiple lung metastases from a colon adenocarcinoma who achieved a complete radiological response after 12 mo of treatment: six with chemotherapy plus bevacizumab and six with bevacizumab alone. Bevacizumab alone was continued as maintenance therapy with bevacizumab alone for 44 mo, and patient experienced only a few side effects that were easily managed, and he enjoyed a good quality of life throughout the entire course of treatment.

Bevacizumab in combination with fluoropyrimidine-based chemotherapy is indicated for the treatment of patients with metastatic carcinoma of the colon or rectum, and it is recommended that treatment be continued until disease progression or unacceptable toxicity. However, when used as monotherapy, bevacizumab is not known to induce tumor regression or disappearance[7].

Saltz *et al*[10] reported that the addition of bevacizumab to an oxaliplatin-based regimen in the first-line setting significantly prolonged median progression-free survival (9.4 mo *vs* 8.0 mo; $P = 0.0023$), but did not significantly improve overall survival or the response rate[10]. However, many patients discontinued bevacizumab combined with chemotherapy for reasons other than progression or toxicity. A pre-defined analysis of on-treatment patients showed a much higher magnitude of benefit in progression-free survival for treatment until progression (HR = 0.63) than pre-progression discontinuation (HR = 0.83), which suggests that it is important to continue bevacizumab to maximize the benefit of its addition to chemotherapy[10].

The role of maintenance therapy in mCRC is still controversial. The most recent ESMO consensus guidelines suggest that treatment discontinuation or maintenance are feasible options after 4-6 mo of full-dose first-line therapy[11]. Two randomized trials-MACRO[12], and DREAM[13]-support the role of maintenance with bevacizumab alone[12] or with erlotinib[13].

However, the magnitude of the benefit of maintenance therapy over the discontinuation approach has been addressed in 3 clinical trials, comparing maintenance with complete treatment discontinuation. The CAIRO 3 trial after a 4 mo' period of treatment (CAP-OX plus bevacizumab regimen) randomized not progressive patients to maintenance with capecitabine plus bevacizumab or

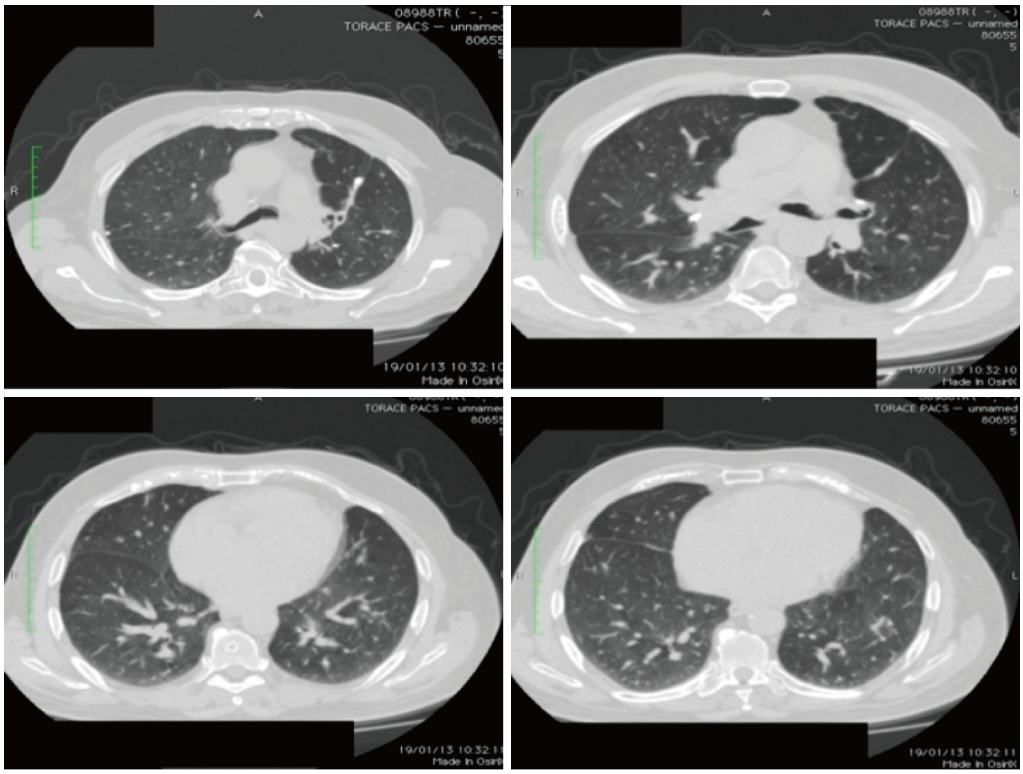

Figure 5 Thorax computed tomography-scan showing the complete response after discontinuing bevacizumab (January 2013).

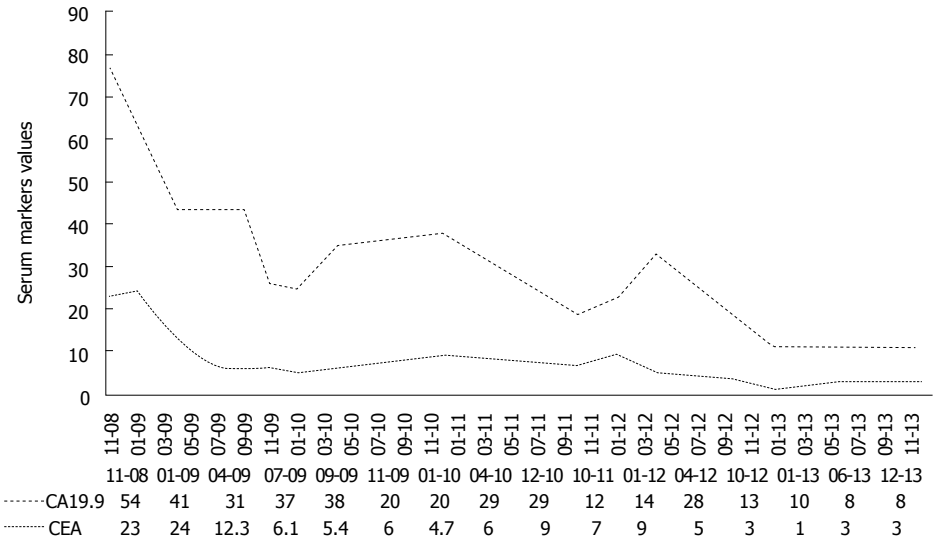

Figure 6 CEA (ng/mL) and CA19.9 (U/mL) serum levels throughout the treatment and follow-up period.

no further therapy. First and second progression-free survival times and time to second progression were improved in the maintenance arm.

The SAKK (41/06) trial was designed to demonstrate the non-inferiority of complete discontinuation of treatment as compared to maintenance with bevacizumab a after 4-6 mo of chemotherapy plus bevacizumab. The non-inferiority was not statistically demonstrated, suggesting that maintenance with bevacizumab might be considered an appropriate option.

At ASCO 2014 the results of AIO0207 were presented. After 24 wk of induction therapy with fluoropyrimidines, oxaliplatin and bevacizumab, maintenance with fluoropyrimidines plus bevacizumab was compared with bevacizumab alone or with complete discontinuation. Maintenance treatment with fluoropyrimidines and bevacizumab prolongs progression free survival and time to failure of strategy with respect to complete discontinuation.

When we decided the maintenance strategy for our patient, there was no information available about the role of fluoropyrimidines in this condition, therefore only be-

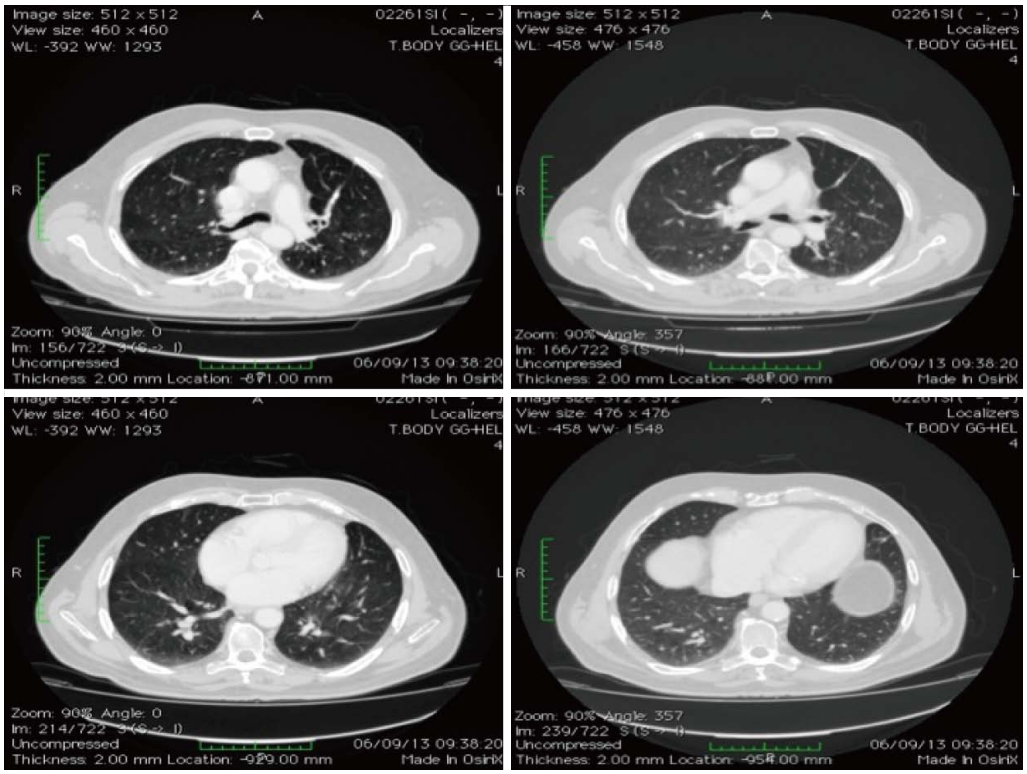

Figure 7 Thorax computed tomography-scan, showing the response at 60 mo since diagnosis (September 2013).

vacizumab was continued. Of note, our patient achieved a complete response after 12 mo of treatment and a very long progression-free survival, which supports continuing bevacizumab after stopping chemotherapy.

Another issue we were able to address is the tolerability of very long treatment with bevacizumab. Our patient was 72-year-old when metastatic disease was diagnosed, and was affected by arterial hypertension. Bleeding, hypertension and venous thromboembolic events are the most frequent side effects of bevacizumab recorded, also in a randomized clinical study[14]. Although hypertension was much more frequent in patients treated with bevacizumab than in controls, only arterial thromboembolic events were significantly higher in the bevacizumab-treated patients aged ≥ 70 years (6.7% *vs* 3.2% in the control group)[14]. It is noteworthy that patients enrolled in clinical trials are selected for their very good conditions, and with very limited comorbidities. However, similar results were in that BRITE observational study, where only a modest increase of arterial thromboembolic events was observed in elderly patients: unadjusted rate per 100 patients-years was 1.4 for patients < 75 years old, 4.0 for patients aged 75-80, and 4.8 for older patients)[15]. Moreover, in the BRITE study, the median time to occurrence of bleeding and arterial thromboembolic events was about 5 mo and the risk of cardiovascular side effects did not increase with the duration of bevacizumab treatment[15].

The AVEX trial[16] was the first phase Ⅲ trial to prospectively evaluate the use of bevacizumab in elderly patients (≥ 70-year-old) affected by mCRC. Bleeding (25.4%), arterial hypertension (19.4%), venous thromboembolic (11.9%) and arterial thromboembolic events (4.5%) were the most common all-grade adverse events in the cohort of 140 patients receiving bevacizumab[16].

In our patient, arterial hypertension worsened after the first administration of bevacizumab, and was successfully managed with anti-hypertensive therapy, without discontinuing bevacizumab.

In conclusion, our report, although based on a single patient, supports the feasibility and, possibly, the benefit of continuing bevacizumab as maintenance treatment for a very long period. Moreover, the case reported here suggests that this regimen can be administered even in elderly patients provided they are fit. Indeed, they can have the same benefits as adult subjects, possibly without a significant increase in toxicity.

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COMMENTS

Case characteristics

The case reports the clinical case of a colorectal cancer patient presenting with lung metastases.

Clinical diagnosis

He underwent first line chemotherapy with capecitabine, oxaliplatin and bevacizumab as induction treatment for six months, after which he continued receiving bevacizumab monotherapy for more than three years.

Treatment

He achieved a complete response and is currently free from relapse.

Experiences and lessons

The long progression-free survival time and the absence of side effects indicates that bevacizumab-based maintenance treatment is beneficial in mCRC patients. However, although some studies reported a benefit of maintenance therapy in PFS or TTF, the definite role of maintenance on survival and the best maintenance regimen might be further investigated in properly designed clinical trials.

Peer review

It is a very interested topic for physicians of multiple specialties such as Internal Medicine, Oncology, Surgery, Family Medicine. The manuscript is very well written.

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CASE REPORT

Acute abdomen in pregnancy due to isolated Fallopian tube torsion: The laparoscopic treatment of a rare case

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Abstract

In the last years, operative laparoscopy became a standard approach in gynaecology and general surgery. Even in pregnancy its use is becoming more widely accepted. In fact, it offers advantages similar to those in no pregnant women, associated with good maternal and fetal outcomes. Around 0.2% of pregnant women require abdominal surgery. The most common indications of laparoscopy in pregnancy are cholelithiasis complications, appendicitis, persistent ovarian cyst and adnexal torsion. Authors describe a very rare case of acute abdomen due to isolated Fallopian tube torsion in a 24th weeks pregnant woman, managed by laparoscopic salpingectomy.

Key words: Fallopian tube torsion; Acute abdomen; Pregnancy; Laparoscopy

Core tip: Authors describe a very rare case of acute abdomen due to isolated Fallopian tube torsion in a 24th weeks pregnant woman, managed by laparoscopic salpingectomy. In all literature the most recent estimation for its incidence dates from 1970, when Hansen estimated 1 per 1.5 million women to have isolated Fallopian tube torsion in Denmark. And since 1933 only 25 cases of Fallopian tube torsion in pregnant women were described.

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INTRODUCTION

The Fallopian tube torsion is a rare cause of acute abdomen and even more rare during pregnancy. In 1933, Regad)[1] reported 201 cases of tubal torsion, 12% of these occurred in pregnant women (n = 24). Since 1933 until 2013 only 25 cases were described.

The etiology is uncertain, but some authors described factors that could be implicated in the occurrence of Fallopian tube torsion. Some of them are intrinsic of the tube like congenital anomalies or acquired pathology (hidrosalpinx, hematosalpinx, neoplasm, surgery) or autonomic dysfunction and abnormal peristalsis; and other are extrinsic like adhesions, pregnancy, mechanical factors, movement or trauma to the pelvic organs or pelvic congestion[2,3].

Since the Fallopian tube torsion is a rare condition and sporadic cases are reported, its real incidence is unknown, and it seems that it is more frequent in the reproductive age, which is understandable because almost all risk factors are not frequent before menarche or during menopause[3].

The clinical characteristics, the laboratory or the imaging studies are not specific, so the diagnosis is difficult. The acute abdominal pain at the lower quadrants is the most common symptom, with sensitive painful palpa-

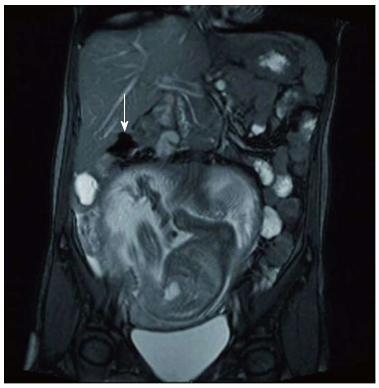

Figure 1 Cystic structure on the right adnexa (magnetic resonance imaging image).

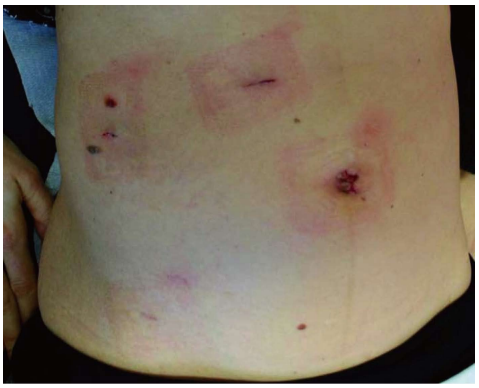

Figure 2 The abdominal sites of the auxiliary trocares.

tion of the same abdominal area. As the clinical and the complementary study are not specific, the definitive diagnosis can be made by laparoscopy. The authors think that, at the present time, laparoscopy in the setting of experienced and dedicated teams should be the standard approach for this situation, even in pregnant women.

We described a case of a 24 wk pregnancy with a right Fallopian tube torsion which was managed by laparoscopic salpingectomy.

CASE REPORT

A 36-year-old healthy primigravida, with an uneventful pregnancy until the 24th week of pregnancy. At this time she complained of a persistent right flank abdominal pain with a sudden increase. Physical examination revealed abdominal enlargement compatible with pregnancy age and a painful right mid abdominal quadrant palpation, with tenderness and without palpable masses.

The ultrasound study revealed a single, life fetus, with a biometry compatible to a 24 wk pregnancy, with normal amniotic fluid volume and with a normal placenta with no signs of abruption; and in the right lower area it showed a cystic structure measuring 4 cm × 3 cm in diameter, probably with an adnexial origin. The MRI confirmed the cystic image, without anyother pathology (Figure 1). Because pain persists, laboratory findings were unspecific and physical examination then was a persisting pain with poor tenderness and peritoneal reaction (acute abdominal pain), two diagnoses were made - acute appendicitis and adnexal torsion.

A diagnostic laparoscopy was then performed. Because the uterus extends 5 cm above the umbilicus, this fact limits the abdomen first entrance, so a direct entrance in the umbilicus could accidental damage the uterus. Alternative Palmer point or the 9th intercostal space is also dangerous because the big pregnant uterus push all the abdominal viscera up. The surgery that we described was an emergent situation, the bowel was not prepared, the viscera distortion was bigger. So the decision was to perform the open technique with the Hasson trocar. The problem was identified by the diagnostic laparoscopy and then the auxiliary trocars were placed underdirect vision and according to the best ergonomic approach for the salpingectomy (Figure 2). We decided to perform a salpingectomy because of the gangrenous aspect of the tube as consequence of its pedicle torsion (Figure 3), without any macroscopic changes of the appendix. The specimen was extracted with a laparoscopic bag. The patient was discharged on the second day after surgery without any complains or surgical and obstetric complication. The reason for two days of hospital stay was based on the diagnosis in a 24th week pregnant woman and immediate control of fetal well-being.

The histopathologic examination of the specimen showed a necrotic tube, secondary of a paraovarian cyst torsion. She delivery a healthy, 3350 g, baby at the 40th week of pregnancy by an instrumental vaccum vaginal delivery because of a progressive distocia at the 2nd stage. No maternal or fetal complications occurred at the peripartum period.

DISCUSSION

Isolated torsion of Fallopian tube is a very uncommon condition, even more rare in pregnant women. In all literature the most recent estimation for its incidence dates from 1970, when Hansen[4] estimated 1 per 1.5 million women to have isolated Fallopian tube torsion in Denmark. And since 1933 only 25 cases of Fallopian tube torsion in pregnant women were Described[2,5,6]. Since this is a very rare situation, probably the series published underestimate the real incidence of this pathology.

Other aspect hard to describe is its etiology. Its real cause is uncertain and it can happen in healthy tubes, but some risk factors were described as possible causes. This factors were divided in two types: internal or intrinsic like congenital anomalies (excessive length of tube or spiral course), acquired pathology (hidrosalpinx, hematosalpinx, neoplasm, surgery) or autonomic dysfunction and abnormal peristalsis; and external or extrinsic factors such as changes in neighboring organs (neoplasm, adhesions, pregnancy), mechanical factors, movement or trauma to the pelvic organs or pelvic congestion[2,3,7].

Although the clinical characteristics are not exclusive

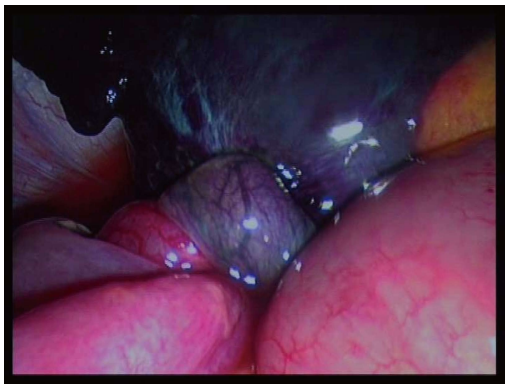

Figure 3 The pedicle torsion of the right Fallopian tube.

of the Fallopian tube torsion, the most common symptom is the lower abdominal pain, generally with a sudden onset and accompanied by nausea, vomiting or urinary urgency[2,3]. Physical findings include abdominal tenderness, with or without peritoneal signs and an inconstant palpable mass[2,3].

All this clinical signs and symptoms are common with other medical conditions and give the physician a differential diagnosis problem, which includes ovarian torsion, acute appendicitis, ectopic pregnancy, acute salpingitis, tuboovarian abscess, ruptured ovarian cyst, degenerated leiomyoma, urolithiasis, intestinal obstruction or perforation[7-9]. Laboratory values are nonspecific and do not help in the differential diagnosis[7,9]. The sonographic findings of isolated Fallopian tube torsion are not pathognomonic and are quite variable[9], especially in second and third trimesters of pregnancy, where the adnexas are more difficult to visualize. But the finding of a high impedance or absence of flow in a tubular structure, especially in a patient with a history of tubal ligation, can be indicative of the diagnosis[10,11].

Pre-operative diagnosis of tubal torsion is very difficult and as its management is surgical the diagnostic laparoscopy is the tool for the definitive diagnosis and treatment[3], even in advanced pregnancies, like the case described.

Until now, there are no prospective and randomized studies that compared laparoscopic procedures with laparotomy during pregnancy. Retrospective studies published, show that laparoscopy in pregnancy appears safe and can be performed without a considerable increment in maternal and fetal complications. Mathevet *et al*[12] published the results of 48 laparoscopic procedures for management of adnexal masses in pregnancy (17 cases were performed during the first trimester, 27 cases in the second trimester and 4 in the third trimester). Except one fetal loss 4 d after surgery, no complications were observed during the intra and post-operative periods and obstetrical outcomes were. So the authors concluded that laparoscopic management of adnexal masses in pregnancy is a safe and effective procedure, performed by an experienced team. Similar conclusions were made by Lenglet *et al*[13] in a series of 26 pregnant patients who underwent the laparoscopic surgery of ovarian cysts.

Despite the limited data, it seems that laparoscopic surgery in pregnancy, in experienced hands, is a technique acceptable with some advantages, including early return of bowel function, early ambulation, short hospital stay, rapid return to normal activity, low rate of wound infection and hernia and less pain after the procedure[14,15]. Another advantage of laparoscopy is the lesser manipulation of the uterus which leads to less uterine contractions, so less spontaneous abortion, preterm labor and premature delivery[14]. However laparoscopy during pregnancy should be performed with caution and some precautions should be taken like: routinely intraoperative fetal monitoring, attention with patient position (for example, the lateral decubitus position should be preferred to prevent inferior vena cava compression), the Hasson trocar open technique seems to be safer to prevent inadvertent puncture of the uterus (but no studies showed a real advantage under the Veress technique), intra-abdominal pressure should be kept less than 15 mmHg, maternal end- tidal volume CO_2 should be monitored and kept within the normal range, depending on the height of the uterus the secondary trocars should be inserted under direct vision and their position decided according to the uterus size and the position of the abnormal findings. The administration of prophylactic tocolytics is not necessary; it can be given if there is evidence of uterine contractions[14,16].

In conclusion, isolated Fallopian tube torsion should be considered as a possible diagnosis of acute abdominal pain in pregnancy. The diagnostic laparoscopy is the gold standard for its definitive diagnosis and allows the tube torsion resolution with a minimal invasive technique, even in pregnant women.

COMMENTS

Case characteristics

Acute abdómen in pregnancy, diagnostic challenges.

Clinical diagnosis

Abdominal enlargement compatible with pregnancy age and a painful right mid abdominal quadrant palpation, with tenderness and without palpable masses.

Differential diagnosis

Laboratory and image exams, high clinical suspicion.

Imaging diagnosis

Ultrasonnography in first approach, magnetic resonance imaging confirmation.

Pathological diagnosis

Histology validates the findings.

Treatment

Laparoscopy, diagnostic and treatment.

Experiences and lessons

Laparoscopy in experienced hands might be the gold standard approach in acute abdómen in pregnant woman.

Peer review

In this case report, the authors highlighted the useful of laparoscopic approach for emergent abdominal surgery in pregnant women. Their assertion is acceptable and the manuscript is well written.

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CASE REPORT

Rare etiology of mechanical intestinal obstruction: Abdominal cocoon syndrome

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Abstract

Abdominal cocoon syndrome is a rare cause of intestinal obstruction with unknown etiology. Diagnosis of this syndrome, which can be summarized as the small intestine being surrounded by a fibrous capsule not containing the mesothelium, is difficult in the preoperative period. A 47-year-old male patient was referred to the emergency department with complaints of abdominal pain, nausea, and vomiting for two days. The abdominal computed tomography examination detected dilated small intestinal loops containing air-fluid levels clustered in the left upper quadrant of the abdomen and surrounded by a thick, saclike, contrast-enhanced membrane. During exploratory surgery, a capsular structure was identified in the upper left quadrant with a regular surface that was solid-fibrous in nature. Abdominal cocoon syndrome is a rarely seen condition, for which the preoperative diagnosis is difficult. The combination of physical examination and radiological signs, and the knowledge of "recurrent characteristics of the complaints" that can be learned by a careful history, may be helpful in diagnosis.

Key words: Intestinal obstruction; Abdominal cocoon syndrome; Preoperatively diagnosis; Adult patient

Core tip: Abdominal "cocoon" is an extremely rare cause of small bowel obstruction. It should be thought of as a rare cause of small bowel obstruction. Its diagnosis is rarely made preoperatively. It has been reported mainly in young adolescent women. But in this adult patient, the small bowel is encased in a fibrous sac called an abdominal cocoon. The clinical manifestations of abdominal "cocoon" are non-specific. The combination of physical examination and radiological signs, and the knowledge of "recurrent characteristics of the complaints" which can be learned by a careful history, may be helpful in diagnosis. Surgery remains the main stay of treatment with satisfactory outcome.

Uzunoglu Y, Altintoprak F, Yalkin O, Gunduz Y, Cakmak G, Ozkan OV, Celebi F. Rare etiology of mechanical intestinal obstruction: Abdominal cocoon syndrome. *World J Clin Cases* 2014; 2(11): 728-731 Available from: URL: http://www.wjgnet.com/2307-8960/full/v2/i11/728.htm DOI: http://dx.doi.org/10.12998/wjcc.v2.i11.728

INTRODUCTION

Abdominal cocoon syndrome, which was first defined in 1978[1], is relatively rare, with descriptions in the literature

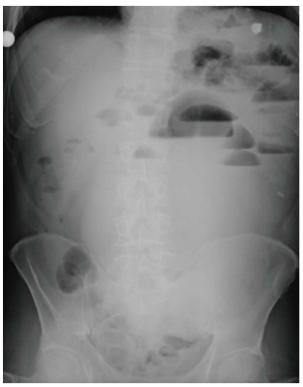

Figure 1 Abdominal radiography, multiple air-fluid levels are seen, which was more prominent in the left upper quadrant.

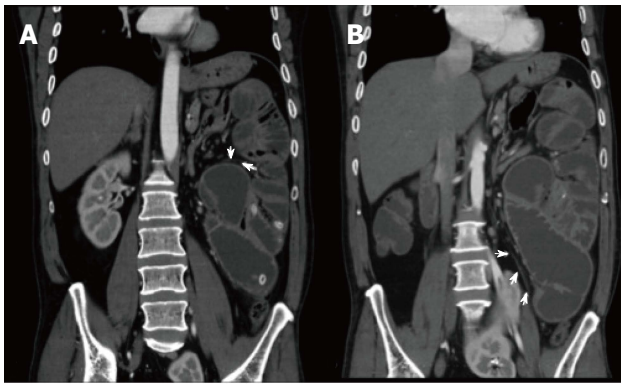

Figure 2 Abdominal computerized tomography - coronal section; dilated small intestinal loops containing air-fluid levels clustered in the left upper quadrant of the abdomen and surrounded by a thick, saclike, contrast-enhanced membrane in the sections close to the root of mesentery (white arrows). A: Superior; B: Inferior.

limited to case reports. In this syndrome, a portion or all of the small intestine is surrounded with a fibrocollagenous membrane not containing the mesothelium. As it is rarely seen, and its clinical findings nonspecific, it is generally diagnosed during surgery[2]. However, it can be characterized by the membrane surrounding the small intestine with contrast-enhanced abdominal computerized tomography (CT) during the preoperative period. Surgical treatment that releases the small intestine by cutting away the adhesions after excision of the membrane is the basic intervention in these cases. This article presents a case with abdominal cocoon syndrome diagnosed, following recurrent complaints, with abdominal CT during the preoperative period and surgically treated.

CASE REPORT

A 47-year-old male patient was referred to the emergency department with complaints of abdominal pain, nausea, and vomiting for two days. The detailed medical history of the patient, who did not have a known chronic systemic disease or a previous history of any abdominal procedures, revealed similar complaints dating back several years that recurred at certain time intervals and had been

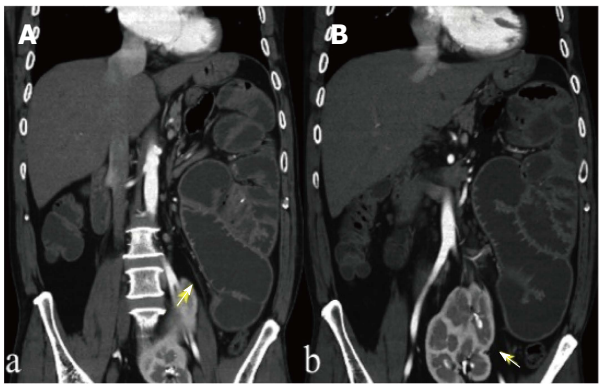

Figure 3 Abdominal computerized tomography - coronal section; dilated small intestinal loops containing air-fluid levels clustered in the left upper quadrant of the abdomen and surrounded by a thick, saclike, contrast-enhanced membrane (A) (arrow). The left kidney was also located ectopically at the midline in the abdomen at the level of the pelvis (B) (arrow).

treated. Upon physical examination, there was asymmetrical distension and general tenderness, especially prominent in upper regions of the abdomen, with heightened intestinal sounds. The laboratory examinations were normal, except for leukocytosis (14.300 mm^3). Multiple air-fluid levels were detected on abdominal radiography, which was more prominent in the left upper quadrant (Figure 1). The abdominal CT examination detected dilated small intestinal loops containing air-fluid levels clustered in the left upper quadrant of the abdomen and surrounded by a thick, saclike, contrast-enhanced membrane. The left kidney was also located ectopically at the midline in the abdomen at the level of the pelvis (Figures 2 and 3). During exploratory surgery, widespread adhesions with the peritoneum and small intestine could not be seen. Upon further exploration, a capsular structure was identified in the upper left quadrant with a regular surface that was solid-fibrous in nature. Only 20 cm of the jejunal and ileal segments in the proximal and distal portions of the small intestine were intra-abdominally localized. The remaining small intestinal segments were inside this structure and the greater omentum was hypoplastic (Figure 4). When the capsule was opened, the small intestinal segments inside the capsule were dilated due to obstruction but otherwise normal in structure. The obstruction was caused by fibrous bands of irregular thickness inside the capsule. The operation was completed after total excision of the capsule and removal of the adhesions. The patient manifested clinical signs of ileus on postoperative day 3 due to the adhesions. He was medically treated with nasogastric decompression and parenteral nutrition and discharged on postoperative day 12 without any problems. Upon histopathological examination, a nonspecific inflammatory reaction in conjunction with fibrous connective tissue proliferation was found. On the third month of his follow-up, the patient did not report any problems.

DISCUSSION

Abdominal cocoon syndrome is a rare cause of acute or

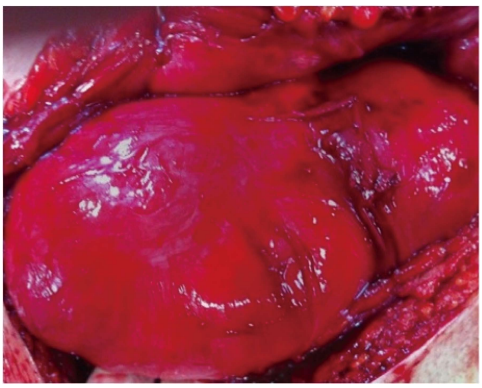

Figure 4 Intraoperative findings; small intestine could not be seen, a capsular structure was identified in the upper left quadrant with a regular surface that was solid-fibrous in nature.

subacute intestinal obstruction, and its' classified as primary (idiopathic) and secondary. Although the etiology is not precisely known, conditions that result in chronic asymptomatic peritonitis (such as: the use of practalol, peritoneal dialysis, endometriosis, and abdominal tuberculosis) are risk factors. Moreover, accompanied by some diseases (systemic lupus erythematosus, familial Mediterranean fever, infections of the Fallopian tubes, retrograde menstruation) have also been reported[3-6] . In a two-case series reported by Yeniay *et al*[7], the greater omentum was absent, suggesting that genetic factors may also play a role in the etiology. Our case reports the role of genetic factors since our patient developed chronic peritonitis without having any of the known risk factors, the greater omentum was hypoplastic, and there was a locational abnormality in the left kidney.

The clinical presentation of abdominal cocoon syndrome is generally acute or subacute intestinal obstruction. There is an increase in intestinal sounds and abdominal distension on physical examination. However, abdominal distension may be asymmetrical, as the small intestine is surrounded by a membrane and not mobile[8]. Common complaints during patient history include the recurrence of nonspecific symptoms such as nausea and vomiting that spontaneously recover or respond to medical therapy. Chronic constipation, anorexia, weight loss, and intra-abdominal masses rarely present in these patients[9]. In the current case, there were signs of intestinal obstruction associated with asymmetrical distension during the physical examination of the abdomen.

As it is rarely seen and the clinical symptoms are nonspecific, diagnosis in the preoperative period is difficult. Clusters of intestinal loops and a surrounding membrane in contrast-enhanced abdominal CT, especially multislice CT, are diagnostic[10]. An abdominal CT that is performed during the preoperative period provides both diagnosis and differential diagnosis, and determines the associated congenital changes, such as the midline location of the left kidney in our case. This prevents undesirable complications during surgery. However, in spite of all opportunities, preoperative diagnosis is difficult and requires advanced radiological experience. In a retrospective study of twenty-four cases, it was reported that only 16% of the cases could be preoperatively diagnosed[11].

There is a consensus that surgical treatment is ideal in these patients. The recommended procedure excises the membrane and unbinds the adhesions between intestinal segments[7,10]. However, this process requires great care, due to the general possibility of secondary damage, as there are extensive adhesions between the membrane and between the intestinal segments. Bowel perforation, enterocutaneous fistula or sepsis occurring as a result of secondary damage, are among the complications that can be encountered during the postoperative period[3]. The recurrence of the cocoon in the postoperative period is rare but the most probable complication is the obstruction of small intestine due to adhesions. The current case revealed clinical signs of ileus during postoperative day 3 that responded to medical therapy.

In conclusion, abdominal cocoon syndrome is a rarely seen condition, for which the preoperative diagnosis is difficult. The combination of physical examination and radiological signs, and the knowledge of "recurrent characteristics of the complaints" which can be learned by a careful history, may be helpful in diagnosis. It should be remembered that medical treatment will not be beneficial and definitive treatment requires careful surgical excision during the early stages of the disease.

COMMENTS

Case characteristics

Patient was referred to the emergency department with complaints of abdominal pain, nausea, and vomiting for two days.

Clinical diagnosis

Upon physical examination, there was asymmetrical distension and general tenderness, especially prominent in upper regions of the abdomen, with heightened intestinal sounds.

Differential diagnosis

The abdominal computerized tomography examination detected dilated small intestinal loops containing air-fluid levels clustered in the left upper quadrant of the abdomen and surrounded by a thick, saclike, contrast-enhanced membrane.

Laboratory diagnosis

During exploratory surgery, widespread adhesions with the peritoneum and small intestine could not be seen.

Imaging diagnosis

Please summarize imaging methods and major findings in one sentence.

Pathological diagnosis

When the capsule was opened, the small intestinal segments inside the capsule were dilated due to obstruction but otherwise normal in structure.

Treatment

The operation was completed after total excision of the capsule and removal of the adhesions.

Term explanation

Early diagnosis is important.

Experiences and lessons

It should be remembered that medical treatment will not be beneficial and definitive treatment requires careful surgical excision during the early stages of the disease.

Peer review

The case report and the discussion are well-written.

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