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Case Series

REMOVAL OF FOREIGN BODIES IN MAXILLARY SINUS, CURRENT TREATMENT OPTIONS AND A CASE SERIES

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ABSTRACT

Foreign bodies in paranasal cavities were a rare finding in the past, but recently the growing demand for dental surgery and cosmetics has increased their number. Treatment is surgical, the aim is to remove the foreign body while minimizing the effect on facial aesthetics. In this article, we analyse the outcomes of 17 patients with diagnosis of foreign body in maxillary sinus treated with different techniques and the pros and cons of said techniques. To remove a foreign body in maxillary sinus and treat sinusitis, if present, the most suited technique seems endoscopy. Caldwell-Luc approach is also an option, however it does not allow to good control over sinusal pathology, it should be considered as a first choice in patients who are not fit or willing for general anaesthesia.

KEYWORDS: *foreign bodies, maxillofacial surgery, otolaryngology, transanal endoscopic surgery*

INTRODUCTION

Foreign bodies inside maxillary sinus were rare findings in the past. Common causes include car accidents, traumatic injuries and improper dental procedures (1-3). Dental roots or whole teeth displaced in maxillary sinus during improper exodontic procedures are the most common, although it is known that teeth can also displace in infratemporal fossa (4). Other possibilities are dental burs, endodontic material, impression materials and recently, as dental implant surgery and other cosmetic dentistry procedure became cheaper and available to a wider portion of the population, whole dental implants (4, 5).

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Adequate preoperative diagnostics procedures should be mandatory to avoid dental implant or tooth migration through the maxillary sinus. Panorex may not be enough when pre-prosthetic, implant surgery or exodontic procedures are planned. Cone Beam Computed Tomography (CBCT) is nowadays the gold standard examination to obtain accurate three-dimensional evaluation of the alveolar bone volume and allow an accurate surgical planning. CBCT allows a three-dimensional analysis of the residual maxillary bone ridge with a sensible detachment of the real residual width of the maxillary sinus floor (6-9).

Endosseous titanium implants have been used for the last four decades with a good rate of success, generally higher in the lower jaw than in the upper jaw. The unique anatomical and physiological features of the upper jaw, like low bone density and quality, centrifugal bone reabsorption and pneumatisation of the sinus that may occur in the edentulous posterior regions (9), make displacement in the maxillary sinus of an implant, as well as tooth or roots during exodontic procedures, not an uncommon event (10-13). Alternatives to conventional implant include zygomatic implants or short implants but these are not devoid of complications (14-16). The use of short implants associated or not to pre-prosthetic trans-alveolar sinus floor elevation, allows implant surgery even if residual bone height is low. Despite this, many practitioners perform these techniques without proper training, increasing the number of implant failure or implant dislocation (17, 18).

It is possible that foreign bodies, usually found in the maxillary sinus, migrate from the maxillary sinus floor to the maxillary ostium. The mucociliary clearance could push the implant out of the maxillary sinus in the middle meatus and, from there, in ethmoid, sphenoid or frontal sinus (19-22). When these complications occur, treatment may not be easy and often requires a multidisciplinary team involving the dentist, the maxillo-facial surgeon and the otolaryngologist.

Caldwell-Luc osteotomy has been the most used approach to access maxillary sinus for over a century (23). Recently functional endoscopic sinus surgery (FESS) has become the gold standard treatment to approach rhinogenic and odontogenic pathologies of the paranasal sinuses due to its lower morbidity if compared to all transoral vestibular maxillary approaches (24-28). Moreover, new applications endoscopy is being studied and applied (29, 30).

Here we present a retrospective study of 17 patients that referred to our Department between 2011 and 2022 to remove foreign bodies from the maxillary sinus including a minimum follow-up of six months.

Description of the clinical techniques

A retrospective study was designed to investigate pathologies and outcomes related to the presence of a foreign body in the maxillary sinus. An electronic data search in a 11-year period between 2011 and 2022 was created. The population included 17 patients aged between 23 and 80 (avg 47.8, SD 16.93), who were referred to the Oral and Maxillofacial Surgery Section of the University Hospital of Verona for diagnosis of foreign body dislocated in maxillary sinus or nonspecific sinonasal symptoms. Among these, 8 (47.06%) were female and 9 (52.94%) were male. The mean follow-up duration was 22.82 months (range 6 to 60).

The inclusion criteria were previous oral surgery to the posterior upper jaw with evidence of radiopaque foreign body in the maxillary sinus in CT scans. After an accurate anamnesis which included previous surgical procedures it was evident that displacement occurred during or after surgical manoeuvres (Fig. 1).

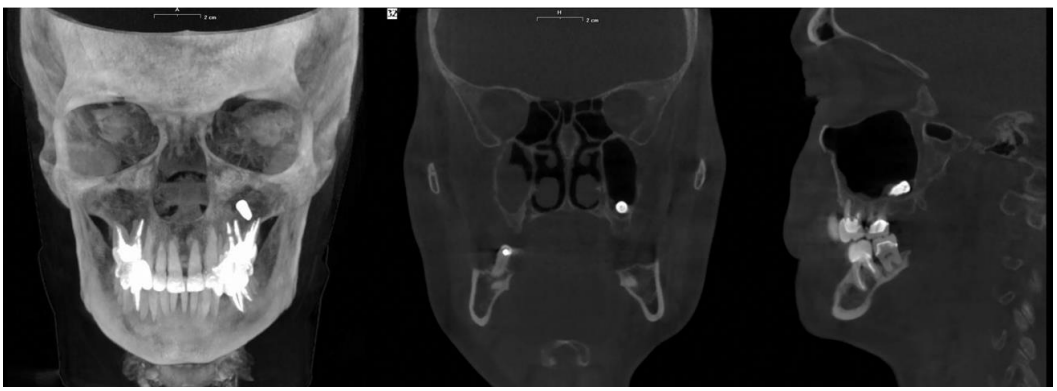

Fig. 1. *Displacement occurred during or after surgical manoeuvres.*

A database with the following data was created: age, gender, smoking habits, type of edentulism, displaced implant/tooth site, implant type (if appliable), intervening time between implant insertion/tooth extraction and detection of foreign body in maxillary sinus, symptoms, sinus lift procedure simultaneous with implant placement; signs and/or symptoms of sinusitis.

The minimum required duration of the follow-up was six months. Depending on each patient's specific needs two type of procedures were planned: Functional Endoscopic Sinus Surgery or Caldwell-Luc.

Given the retrospective aspect of our study our work was exempted by our university ethical institutional review board.

Transnasal endoscopic sinus treatment

All patients underwent surgery after a preoperative antibiotic therapy with ciprofloxacin or amoxicillin and clavulanic acid. The endotracheal tube was positioned through the mouth to allow an adequate endoscopic transnasal approach. Surgery started with the transnasal endoscopic approach that allows an effective evaluation of the diffusion of the infection from the maxillary sinus to the ethmoidal and frontal sinuses. A direct 4-mm 0°, 45° or 70° endoscope was used (Karl Storz GmbH & Co KG, Tuttlingen, Germany).

If the foreign body was directly viewable, it was immediately removed by means of nasal forceps (Fig. 2). Afterwards antrostomy was performed to allow a direct larger view of the maxillary sinus.

If sinusitis was present, it was carefully treated removing all the inflammatory tissues. The anterior or posterior ethmoidectomy and the sphenoidectomy were performed only in case of their direct pathological involvement.

Otherwise, once the foreign body was identified, the head of the patient was turned to the opposite site of the sinus involved. A direct irrigation of the maxillary sinus was performed in order to move the foreign body prior to its removal (Fig. 2).

Caldwell-Luc approach

Patients underwent surgery in local anaesthesia after a preoperative antibiotic therapy with ciprofloxacin or amoxicillin and clavulanic acid. Surgery begins with retraction of the upper lip to expose the anterior wall of the maxillary sinus. A paramarginal incision is performed on the vestibular gum to expose the anterior wall of the maxillary sinus. An osteoplasty of the antero-lateral wall is then performed to gain access to the maxillary sinus and proceed to remove the foreign body. The dimension of the maxillary window is directly related to the dimension of the foreign body and could reach 2cm in case of third molar migration. Gingival incision is then closed with absorbable sutures. Afterwards the patients follow medical therapy with antibiotics and N-Acetylcysteine (Fig. 3).

RESULTS

A total of 17 patients (9 male, 8 female) were included in the study. 3 patients underwent Caldwell Luc approach, 1 underwent a combined Caldwell-Luc and FESS, the remaining 13 undewent FESS. Average age was 49.18 years (SD 15.24), patients treated with FESS (48.15) CL (48.67). 10 patients had radiologic evidence of sinusitis while 7 had no signs of sinusitis. In 11 cases patients had evidence of displaced dental implant, while 6 had evidence of tooth or radicular

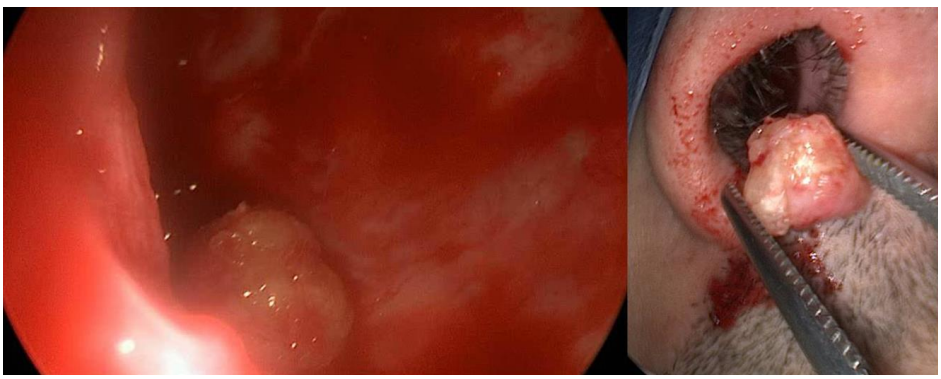

Fig. 2. *Foreign body removal by means of nasal forceps.*

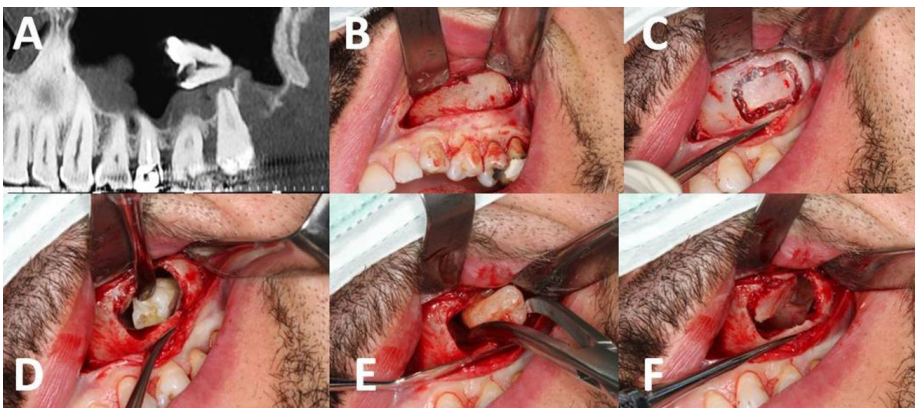

Fig. 3. *Foreign body removal by means of nasal forceps.*

remnant displaced. All displaced implants were originally positioned in posterior sectors (premolar or molar), 3 teeth were molars, 2 premolars and 1 was an impacted canine. Average time between displacement and diagnosis was 24.12 months, (min 0, max 96 months), 22.71 months for patients with sinusitis, and 31.55 for patients without sinusitis.

DISCUSSION

Implant surgery represents today a common dental procedure. As a result, practitioners, with different levels of experience, have also increased, and nowadays these treatments have become more and more popular in everyday practice.

Since both maxillary bone augmentation procedures and endosseous implant computer guided positioning techniques have evolved, it is now possible to position implant in atrophic jaws (6-9). However, with the diffusion of these techniques and a more demanding population, new problems have arisen (31, 32), such as the accidental displacement of these implants inside the maxillary sinus (1-3, 10, 12). Causes are attributable to incorrect surgical planning, improper surgical techniques and inexperience of the surgeon.

An accurate preoperative evaluation is mandatory when planning implant surgery or tooth extractions, CT scans are required to evaluate thickness and density of the maxillary bone (6, 8). In case of atrophic (class III-IV) maxilla it is possible to use short implants(17,18,19), in case of more severe condition (class IV-VI) bone grafts should be performed prior implant insertion, while in case of extreme maxillary atrophy zygomatic implants are the best therapeutic option (7, 33, 34).

At present CBCT represents the goal standard in implant oral positioning planning. The use of CBCT is mandatory because it allows the surgeons to evaluate the precise three-dimensional dimension of the residual alveolar bone. The use of CBCT is indicated in the preoperative planning as well as in the postoperative control. CBCT obtains an accurate morphological description of the bony structures and then its use is also indicated in case of foreign body migration trough the paranasal sinuses (1, 6-9).

There are not many experiences described in literature about the surgical treatment of foreign bodies dislocated in maxillary sinus (25-28, 35). Sgaramella et al. in 2014 carried published a report of 21 patients that referred to the department of head and neck surgery between 1990 and 2010 (1). Our sample, which consists of 17 patients operated between 2011 and 2022 has greater incidence, which reflects the diffusion of implant surgery. Other parameters such as age and gender show no substantial difference.

Although in our sample cylindrical implants are more frequently dislocated, given our relatively small sample it is not possible to determine whether this type of implants dislocate more frequently or not. The difference could be attributed to the fact that cylindrical implants are more common in upper jaw implant surgery. The most common implant site involved in our case series was the upper first molar probably because of its thinness in of the upper atrophic jaw (8, 9).

The other main causes of foreign bodies in maxillary sinus were tooth extractions. It is possible that, during exodontic procedures, the tooth dislocates in maxillary sinus. In our sample 5 out of 6 dislocated teeth were caused by the extraction of upper premolar or molar tooth while in one patient the cause was an impacted canine tooth.

Sinusitis shows positive association with dislocated foreign bodies, this may be caused by foreign bodies that are infected with intraoral flora which is different from nasal and paranasal flora. Moreover, the presence of a foreign body inside paranasal sinus can alter the physiological mucociliary clearance creating stagnation of mucus that gets infected more easily. It is also known that smoking may slow down clearance and promote sinusitis, in our sample this association is present (57% sinusitis in nonsmokers vs 66.67% sinusitis in smokers) but not statistically relevant ($p>0.05$).

The mucociliary clearance could push the implant out of the maxillary sinus in the middle meatus and, from there, in ethmoid, sphenoid or frontal sinus (19-22). Whenever a foreign body migrates out of the maxillary sinus, there is an immediate indication to the surgical removal of the foreign body.

Current guidelines for the removal of foreign bodies in maxillary sinus depend on the timing of the dislocation. For implants that dislocated during surgery, removal is possible immediately. it is recommended to remove as soon as possible through the same path used to perform implantology while the endoscopic approach is indicated only if the transoral approach is ineffective.

If implant dislocated long time after implantology the surgical approach should be focused on the removal of material from the sinus and the prevention of possible consequences inside the sinus. For this reason FESS is nowadays the gold standard surgical treatment for nasal and paranasal cavities due to its characteristics (11).

It has a low morbidity compared to other techniques since it does not require any large osteotomy which may cause damage to the infraorbital nerve or cause damage to the apical region of the teeth. It is less invasive, unlike other techniques, it does not leave scars neither on the skin nor on the gum, it also does not require any suture at all. On the other hand, FESS has some disadvantages. The materials to perform this kind of surgery are more expensive that traditional instruments and they can be used only to perform endoscopic surgery, it requires a short hospitalization and general anaesthesia. Endoscopic surgery is a relatively difficult procedure and requires a specific training which can be obtained only in specialized centres.

Caldwell-Luc is nowadays considered a second line treatment to approach paranasal cavities. It is faster and does not require any specific training, but most importantly, it does not require general anaesthesia. Therefore, it can be used in patients that cannot general anaesthesia or those who are unwilling to undergo this procedure. It also allows a wider opening to perform surgery inside maxillary sinus, which can be required if a large foreign body is dislocated inside maxillary sinus (11, 23). On the downsides Caldwell-Luc procedure is related to a higher rate of complications such as silent sinus syndrome, lesion of the infraorbital nerve and ineffective sinusitis healing. Moreover, bone loss of the lateral wall of the maxilla may lead to an unfavourable prognosis in case of pre-prosthetic surgery or dental implant surgery and can generate facial asymmetry.

Foreign bodies in maxillary sinus are an uncommon event in clinical practice and most of the times they are the result of iatrogenic damage. Short-time implant failure/dislocation can be avoided by an accurate preoperative evaluation, a good surgical plan and, ultimately, experience.

Long-time implant dislocation is more difficult to prevent. Biological systems have too many variables that are unknown, unpredictable or not present at all at the time of the surgery, therefore, even if a proper preoperative evaluation is carried out, implant dislocation is still possible.

The presence of radicular remnants, burrs etc inside maxillary sinus is the result of malpractice, faulty materials, incorrect surgical planning or inexperience. These events are almost all preventable by proper planning, usage of quality materials and experience.

Since endoscopic surgical techniques have evolved it is now possible to perform foreign bodies removal by FESS, which is also a good option to treat sinusitis and perform a middle meatal antrostomy in the same surgical session.

Caldwell-Luc approach is still a viable solution, it allows for removal of foreign body in local anaesthesia, but it does not allow good control of sinus pathology, if present. This approach should be also used in special cases such as large migrated foreign bodies or patients who are not eligible for narcosis.

Timing of migration represent the keystone in the choose of the surgical approach to remove foreign bodies form

the maxillary sinus. In case of intraoperative migration, the surgeon should always attempt to remove the foreign body through the anatomical pathway that the implant opened to migrate into the maxillary sinus. Wide bony enlargement is contraindicated in order to spare the alveolar ridge profile and the chance of the patient to undergo other dental rehabilitation. If not contraindicated Caldwell-Luc can be attempted in the same surgical session to attempt to salvage the planned treatment. Whenever the intraoperative first attempt isn't successful, the surgeon should refer the patient to a specialist in order to evaluate the feasibility of an endoscopic surgical approach.

The delayed migration of dental implant trough the maxillary sinus doesn't represent an emergency. A CBCT of the paranasal sinuses should be performed in this case to obtain a precise three-dimensional localization of the foreign body into the paranasal sinuses and to limit radiation from conventional CT.

The preferred approach in delayed migration of dental implant is represented by FESS due to its low rate of morbidity and relatively high rate of maxillary sinusitis considering both maxillary bone anatomy and function.

The combined intraoral and endoscopic trans-nasal approach is required whenever both maxillary sinusitis and oroantral fistula are evident. The combined approach in fact allow the surgeon to restore maxillary sinus function and to obtain an effective closure of the oroantral fistula.

CONCLUSIONS

Incidence of foreign bodies displaced in maxillary sinus is increasing due to the increased number of dental cosmetic surgery and other surgical dental procedures. Proper training of the surgeons and surgical planning could reduce the incidence of displaced foreign bodies. FESS should be the preferred choice for foreign bodies removal when maxillary sinusitis is present. Caldwell-Luc approach should be considered in patients with few rhino-sinusal symptoms or patients with symptoms of sinusitis who are ineligible for narcosis.

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Case Report

MANDIBULAR SWELLING IN A PATIENT WITH OSTEOLYTIC LESION: BURKITT'S LYMPHOMA CASE REPORT AND REVIEW OF LITERATURE

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ABSTRACT

Burkitt's lymphoma rarely occurs as a lesion of the oral cavity. Therefore, it must not be excluded from the differential diagnosis in case of worsening swelling of the facial mass. The clinician must know the right diagnostic-therapeutic course to be undertaken with the execution of radiological examinations and a biopsy. Here a case is reported and literature discussed.

KEYWORDS: *Burkitt, sporadic, children, jaw*

INTRODUCTION

Burkitt Lymphoma (BL) represents up to 80% of Non-Hodgkin lymphomas in pediatric patients (1). Three different types of BL have been described: endemic Burkitt Lymphoma (EBL), sporadic Burkitt Lymphoma (SBL) and immunodeficiency related Burkitt lymphoma (IRBL). EBL (also knowns as African variant) is related to chronic Epstein-Barr virus infection, since up to 50% of the EBL patients have mandibular manifestation (2, 3). SBL (non-African variant) mainly manifests as an abdominal mass and only 9% of cases have oral manifestations. IRBL is associated with acquired

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immunodeficiency (HIV infection, transplant patients, etc) (4, 5). The mandible is the most affected area in the oral cavity, the posterior sector being more frequently involved than the front sector. Signs and symptoms include facial asymmetry, pain, dysesthesia, dislocation of teeth (3). Early diagnosis and access to proper therapy are essential to increase the survival rate.

CASE PRESENTATION

A patient was referred to the department of head and neck of the university hospital of Verona for a rapidly growing, non-painful swelling of mandibular angle. The patient was a full term born, 4 years old male, no allergies nor active pathologies were reported. An orthopantomogram (Fig. 1) had been performed in another hospital and showed multiple osteolytic lesions of the mandibular angle and dislocation of dental gems and teeth.

A CT scan with contrast was then performed, it showed an osteolytic lesion, highly vascularized which was very close to the left mandibular gland, gems of elements 3.6 and 3.7 were dislocated (Fig. 2) and there were other multiple bilateral lesions in cervical lymph nodes, moreover there were similar lesions in axillary lymph nodes bilaterally.

Blood exams were performed and resulted normal; the patient underwent multiple biopsies in general anaesthesia. The histological exam revealed "fragments of soft tissue and bone with lymphoid tissue mixed with macrophages with "starry-sky" appearance".

Immunohistochemistry analysis test positive for CD20, CD10, c-myc and showed high replication index (ki67>90%), while blc2, TdT, CD34, Desmin, Vimentin, and cytokeratin 8-18 tested negative. Fish-test tested positive for fusion of cmyc-igh (t8;14), the final diagnosis was Burkitt Lymphoma. A full-body PET was then performed to complete the staging of the disease, it confirmed the known lesions and did not reveal any other lesion (Fig. 3), then the patient underwent bone marrow biopsy and cerebrospinal fluid sampling. Both tests were negative.

Chemotherapy was programmed and carried out according to protocol AIEOP LNH, group R2. At the end of the chemotherapy a new CT scan with contrast was performed after the chemotherapy, structural alterations of the mandible were absent and lesions in cervical and axillary lymph nodes showed signs of regression. At 1 year follow-up the patient was still disease-free and is currently in follow-up.

Literature review

This review was carried out with a narrative approach that can allow highlighting main findings of literature about the specific topic to outline and to improve knowledge in this field.

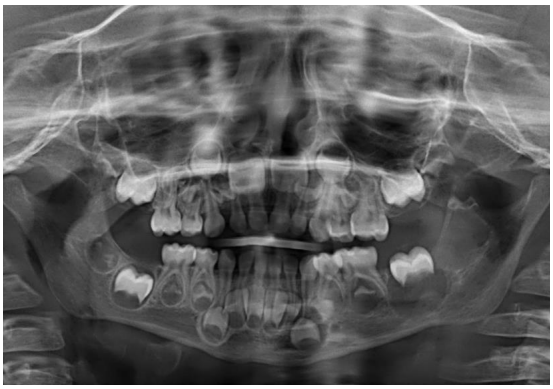

Fig. 1. *Orthopantomogram performed showing multiple osteolytic lesions of the mandibular angle and dislocation of dental gems and teeth.*

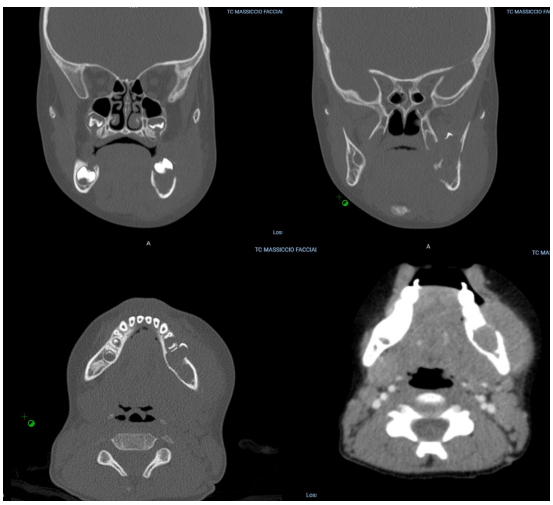

Fig. 2. *CT scan with contrast showing osteolytic lesion.*

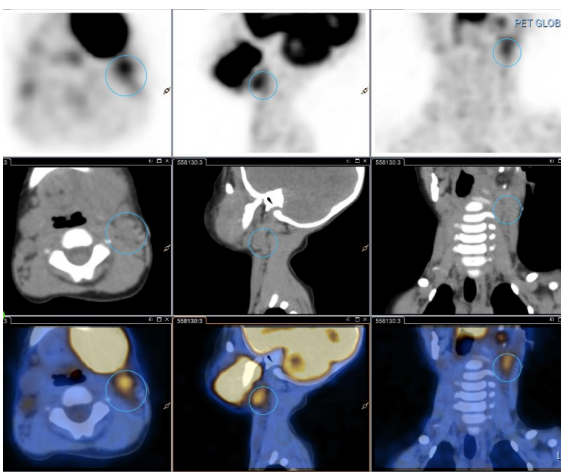

Fig. 3. *Full-body PET confirming the known lesions not revealing any other lesion.*

Specifically, concepts proposed by Egger et.al were pursued to perform narrative review of the literature according to the following steps (Table I).

Step I: formation of a four-member working group. Each of them performed as methodological reviewer and all of them were clinical experts.

Step II: Formulation of review questions derived from up-to-date findings of case reports of sporadic Burkitt lymphoma in pediatric patient clinical features and treatment choices. This represents a pivotal step to effectively build a search strategy.

Step III: using keywords "non endemic Burkitt lymphoma" and "sporadic Burkitt lymphoma" to perform search in databases (PubMed, PMC). Boolean operators as well as the Mesh terms were not applied to minimize potential restrictions in finding results. Inclusion article criteria were original articles, related only to humans, without limitation of publication date, no limitation about the study design were applied. Exclusion article criteria were articles for which full text was not available, were not in English, or were grey literature, adult case report. Reviews and meta-analyses were excluded. Duplicate articles were eliminated and, from the articles retrieved in the first round of search, additional references were identified by a manual search among the cited references. Process of literature selection was reported following the PRISMA statement guidelines. To clarify the topics of this review, outcomes were identified as follows: presence of orbital metastasis from breast cancer (clinical and/or radiological signs and symptoms) with histopathological identification of primary tumor and presence of protocol for the treatment of the patients.

Step IV: analysis of all data extrapolated was carried out by authors and Table II was designed to present data in form of narrative review in the results section of this paper.

RESULTS

The considered articles were all case report. Studies' year of publication ranged from 1991 to 2022.

The papers included 15 patients overall, 93% of which were male. Patient's age ranged from 3 to 16 years old with an average of 10 years old. Jaw swelling was present in 3 of the cases (20%), of which 2 (13.5%) had maxillary sinus involvement and 1 (6.5%) jaw affected, 73% of the patients had also abdominal involvement. The most used imaging was CT (67%) while MRI was used in 26%. Chemotherapy was used in all cases, while surgery only in 1 and radiotherapy in 2 cases. Finally, follow up was between 5 month and 12 years.

Table I. *Methodological approach to review*

Step	General Activities	Specific Activities
I	Formation of working group	*Four maxillo-facial surgeon expert in head and neck anatomy, as clinical and methodological operators*
II	Formulation of the review questions	Evaluation of case reports of sporadic Burkitt lymphoma in pediatric patient. Analysis of main clinical features, demography and treatment choices.
III	Identification of relevant studies on PubMed and PMC	1. Identification of keywords in the field of interest
		2. Use of Boolean operator (AND)
		3. Inclusion criteria: no time limitation for works published; language: English; all types of full text articles. Exclusion criteria: no full text available, reviews of the literature and reviews of the literature with meta-analyses
		4. Elimination of duplicates
		5. Manual search through the references in selected articles
IV	Anaysis and presentation	Extrapolation of data from all revised studies and their presentation in form of narrative review

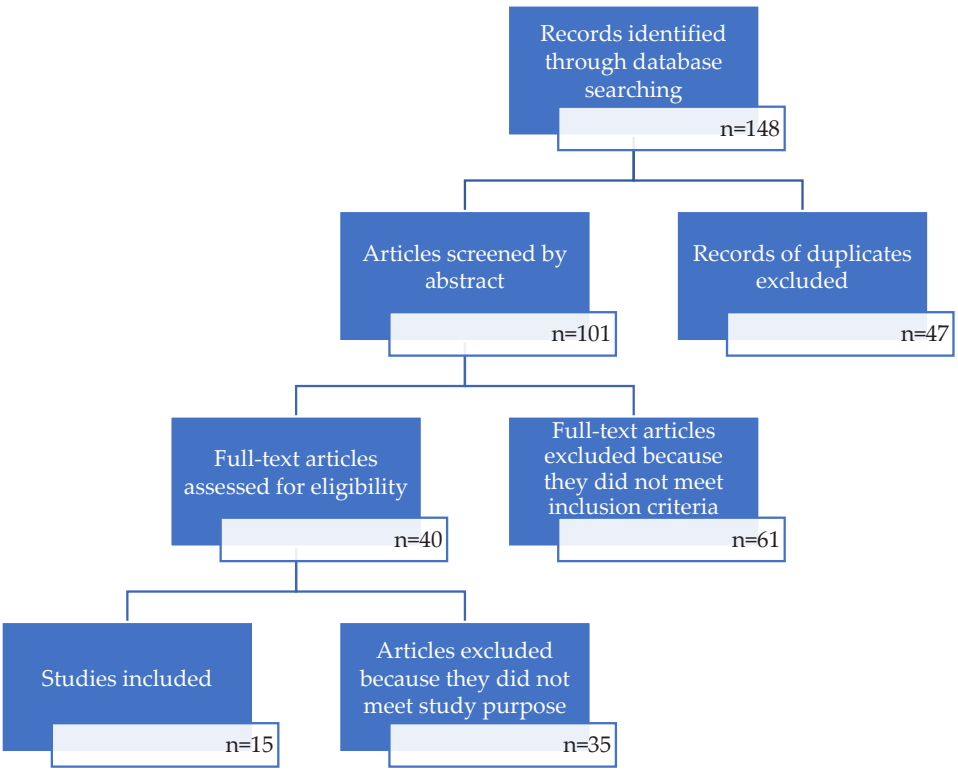

Table II. *Data reviewed.*

DISCUSSION

According to WHO there are 3 variants of BL: endemic, sporadic and immunodeficiency related. The most prevalent is the endemic variant which typically affects males aged between 4 and 7 in Africa (6). Immunodeficiency related variant is associated with HIV infection and other acquired immunodeficiencies such as transplanted patients, it has a rapid progression and usually it involves the bone marrow. Sporadic variant accounts for 3% of all cases of non-Hodgkin lymphoma (7). The head is more frequently affected by the endemic variant, while the sporadic variant mainly affects the abdomen. Only 9% of SBL have oral manifestation and the posterior jaw is the most affected region.

Facial swelling in pediatric patients may be caused by many different pathologies (8) and are frequently cause of great concern among parents given the relative unawareness of the general population regarding neoplasm of the head and neck (9).

Early treatment is extremely important because these pathologies are serious and can have a rapid development, differential diagnosis include: metastatic neuroblastoma, rhabdomyosarcoma, osteosarcoma other NHL and leukaemia (10, 11).

Symptoms are painful swelling, paraesthesia of inferior lip/chin (numb chin syndrome), facial asymmetry, dislocation of teeth or dental gems. The first step to assess facial swelling should be radiologic assessment of the lesion (12-14) (by orthopantomogram CT or MRI), signs of BL are osteolysis, irregular borders and dislocation of teeth(15). Afterwards a biopsy is required for a proper diagnosis, and, if BL is confirmed, PET and total body CT are required for proper staging of the disease.

Therapy for Burkitt Lymphoma is a combination of different chemotherapy agents (cyclophosphamide, vincristine, methotrexate, prednisone, cytarabine, etc.) which can be associated or not with rituximab (1, 15). Surgical resection is limited to few cases in which it is possible to achieve resection of the disease without delaying the systemic therapy(18). Survival rate is generally high in early/mild stage (up to 98%) treated with chemotherapy, while in more advanced stages it drops to 95%. Relapse is more frequent in the first 2-3 years with a peak in the first year (16, 18).

CONCLUSIONS

The case of Birkitt's Lymphoma of the mandible outlined that a multidisciplinary approach is essential to perform an early diagnosis and a proper therapy therefore increasing chances of survival (18). Head and neck specialists should be involved in the diagnostic path, moreover they should be aware of this type of neoplasm. They should also be involved on the follow-up process to treat unfavourable dento-skeletal and aesthetic outcomes.

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Case report

INTERNAL-EXTERNAL LARYNGOCELE TREATED WITH EXCLUSIVELY TLM: HOW I DO IT.

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KEYWORDS: *laryngocele, Transoral Laser Microsurgery, TLM, minimally invasive surgery*

ABSTRACT

Laryngocele is a rare pathology with different grades of extension. Minimally invasive surgery, such as Transoral Laser Microsurgery, is also widely used for combined laryngocele (with internal and external components). In this paper, we show the step-by-step procedure for the treatment of a combined laryngocele with Transoral Laser Microsurgery. This technique allows us to obtain good clinical results: complete removal of the disease, short hospitalization, low morbidity, and rapid recovery. At clinical evaluation after three months, the patient showed no recurrence of the disease.

INTRODUCTION

A laryngocele is an abnormally dilated laryngeal saccular cavity that may be filled with air (classic laryngocele), mucus (laryngomucocele), or purulent secretions (laryngopyocele). Laryngoceles are classified as internal, which is confined to the endolarynx, external, which extends beyond the borders of the laryngeal cartilages, and combined, which has an internal and external component (1). It may be the result of a repeated increase in pressure in the upper respiratory tract, as may occur in glass workers or players of wind instruments; in rare cases is associated with occult squamocellular glottic carcinoma (2).

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Laryngocele is a rare condition. According to recent data, the incidence of the disease is 151 per 2.5 million people per year (1). The highest incidence is observed in the sixth decade of life, with a predominance in the male sex (males: females = 3:1). Nearly half of the laryngoceles are discovered incidentally, such as during head and neck examinations or CT and MRI examinations for other purposes (3).

Treatment of laryngoceles requires surgery (4). There are several types of surgery, mainly open or transoral. The choice of surgical technique depends on the location and extent of the disease (5), but also the surgeon's experience. Internal laryngoceles are usually treated with transoral procedures only, while external and combined laryngoceles may be treated with a combination of transoral and open transcervical approaches (6). Nowadays, Transoral Laser Microsurgery (TLM) is widely used with good results in external or combined laryngoceles, avoiding open surgery. This approach allows for a reduction of surgical and hospitalization time and surgical complications (7). The aim of this study is to show step by step how to manage a combined internal-external laryngocele with exclusively TLM.

MATERIALS AND METHODS

Before surgery, the patient underwent CT and MRI scans of the neck and fiberoptic endoscopic examination of the internal anatomy of the larynx. These findings provided a reliable assessment of the size of the laryngocele and its relationship to surrounding structures. Appropriate surgical planning can be made only after adequate clinical and radiological examination.

Written informed consent was obtained from the patient, and the surgical procedure was discussed in detail with the patient to inform her of the risks and benefits of the chosen technique. The surgical procedure is performed under general anaesthesia. Removal of the internal and external components of the laryngocele is performed under a surgical microscope and with CO_2 laser (9).

RESULTS

The patient was discharged the day after the procedure, without any particular problems. Since awakening after surgery, the patient breathed and spoke without difficulty. The voice remained unchanged. Food intake was also resumed regularly without any restrictions.

The patient underwent endoscopic follow-up 1 month and 3 months postoperatively. At the last checkup, a regular surgical result with complete mucosal healing at the laryngeal level was observed. Macroscopically, there were no signs of disease recurrence. In addition, the patient reported no symptoms related to the pathology; specifically, she reported no dyspnea, dysphonia, or dysphagia.

DISCUSSION

The treatment of laryngocele has evolved in recent years. Originally, almost all cases of laryngocele were treated through an open approach with various surgical procedures: transthyrohyoid membrane approach, thyrotomy with resection of the upper third of the thyroid cartilage, and V-shaped thyrotomy (8). Nowadays, the transoral approach is most commonly used because of its numerous advantages. Many authors have demonstrated successful transoral treatment of laryngocele in both internal and combined laryngocele. With increasing use of CO_2 laser (9), TLM is a less invasive technique that can be performed in less time compared with the open technique. Devesa et al (9) performed a retrospective study in which three patients with combined laryngoceles were treated with an endoscopic approach, with no complications and good clinical outcomes. Ciabatti et al (10) have shown that resection with CO_2 laser (9) is currently the preferred technique because it is precise, efficient, and safe compared with an open approach. In addition, the hospitalization of patients treated with the endoscopic procedure lasts only a few days, and patients make a full recovery more quickly. Moreover, there are no relevant effects on swallowing and speech in patients who have undergone endoscopic treatment of laryngocele (11). Patients can speak, drink and eat within a few hours of the procedure, without the need for medications or precautions.

Another surgical procedure that is gaining popularity for combined laryngoceles is transoral robotic surgery (TORS).

As an endoscopic procedure, this surgical technique offers all of the above advantages. In addition, the outer portion of the laryngocele can be better visualized because of its range of motion. However, it should be kept in mind that the choice of surgical technique depends primarily on the particular patient, the type of lesion, and also on the surgeon's skills and preferences.

In summary, the literature shows that the treatment of laryngocele has progressed since its initial description, from an open to an endoscopic approach. Recently, the robotic surgical approach has gained popularity. Nevertheless, the transoral approach with TLM is the first choice for internal laryngocele and selected combined laryngocele.

Surgical technique

In the following, we describe an exclusive TLM approach using CO_2 laser to treat an internal-external laryngocele. The patient underwent general anaesthesia, and a small-diameter reinforced tube was used. After exposure of the larynx with a rigid laryngoscope, the surgical microscope was positioned. The laryngocele was clearly visible through the right ventricular fold.

Step 1: Visualization of the larynx. The bulging at the level of the right ventricular fold, clearly visible, indicates the internal component of the laryngocele (Fig.1);

Step 2: Incision of the upper part of the ventricular fold is performed with CO_2 laser until the capsule of the laryngocele is reached. A small cotonoid is placed to protect the tube (Fig. 2);

Step 3: The laryngocele is then cut, and its glue content is suctioned (Fig. 3);

Step 4: Once empty, the borders of the laryngocele are more clearly visible. At this point, the surgeon begins the detachment of the lateral wall of the capsule by gently pulling it medially (Fig. 4). This step is crucial to allow adequate mobilization, traction, and dissection to completely remove both the internal and external components of the laryngocele;

Step 5: If the external portion of the laryngocele is very deep, it might be useful to adopt a piecemeal dissection technique (Fig. 5);

Step 6: Once the excision is completed, the bottom of the ventricle is clearly visible. In this case, the surgeon preferred to preserve the more medial portion of the ventricular fold to allow better recovery (Fig. 6);

Step 7: Endoscopic inspection (Fig. 7) with an angled rigid 70° endoscope was performed to verify the complete removal of the laryngocele. Control was made 1 month after surgery. Recovery was nearly complete, with no evidence of residual lesion (Fig. 8).

Summary

Laryngocele is a very rare condition that can be life-threatening because it can lead to acute airway obstruction.

Many cases of laryngocele are detected incidentally.

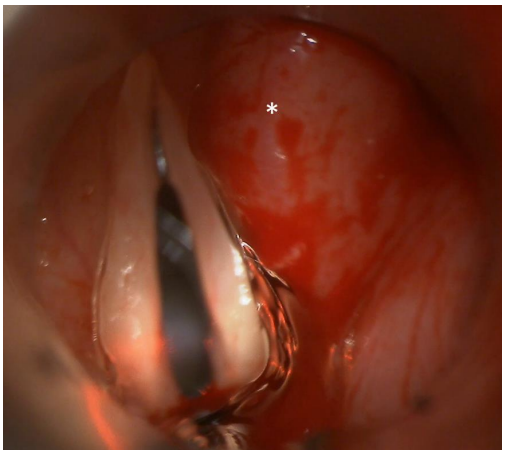

Fig. 1. *Visualization of the larynx.*

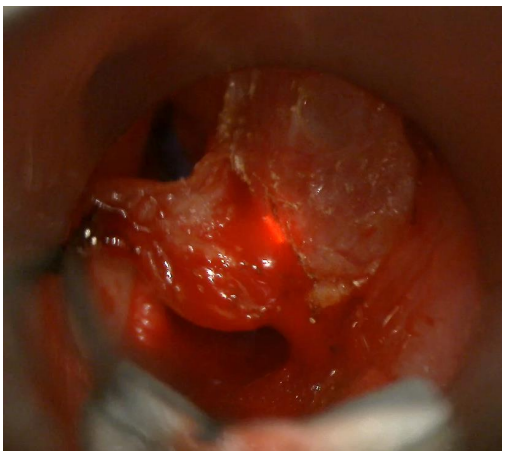

Fig. 2. *Incision of the upper part of the ventricular fold is performed.*

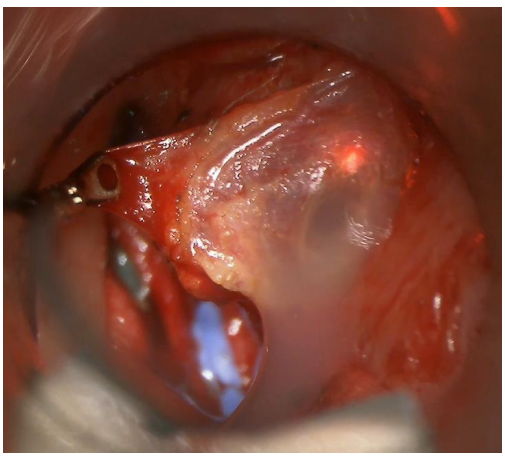

Fig. 3. *Cut of the laryngocele.*

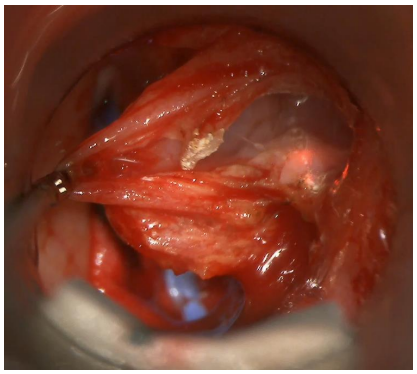

Fig. 4. *Detachment of the lateral wall of the capsule.*

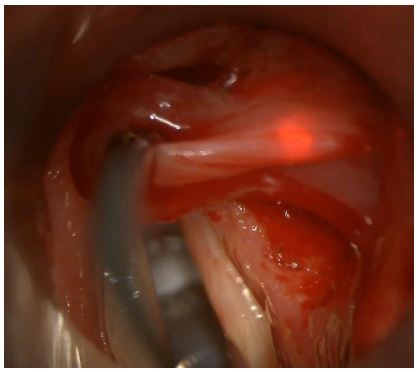

Fig. 5. *dissection technique.*

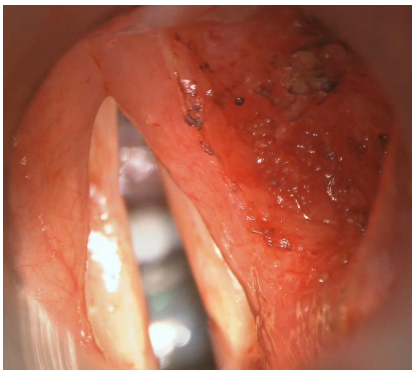

Fig. 6. *the bottom of the ventricle upon completion of the excision.*

Treatment of laryngoceles requires surgery and has evolved in recent years.

Internal laryngoceles are treated with an exclusively transoral approach, whereas combined internal and external laryngoceles are often treated with a combined transoral and open cervicotomic approach.

Surgery is performed under general anaesthesia.

Radiological examination must be performed before surgery to select the best surgical procedure.

The transoral approach with CO_2 laser for combined laryngoceles has fewer complications and morbidities and allows for a faster recovery and shorter hospital stay while maintaining satisfactory clinical outcomes.

There are no relevant effects on swallowing and speech in transorally treated patients.

TORS is becoming increasingly popular for combined laryngoceles.

The choice of surgical technique also depends on the surgeon's skills and preferences.

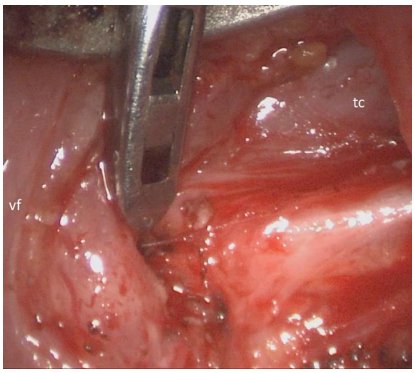

Fig. 7. *Endoscopic inspection.*

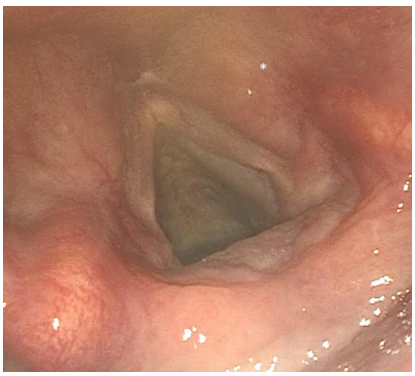

Fig. 8. *Fiberoptic examination at 1 month post-surgery.*

Author contributions

CL wrote the paper; VA edited the images; GM, performed the surgical procedure; RN, LB, GF and LS corrected the paper and supervised the whole work.

Conflict of interest

The authors have no financial relationship to disclose.

Ethical approval

All procedures performed in studies involving human participants conformed to the ethical standards of the Institutional and/or National Research Commission and the 1964 Declaration of Helsinki and its subsequent amendments or comparable ethical standards. The Clinical Trials Ethics Committee of the Provinces of Verona and Rovigo exempted this study from its approval. All authors read and approved the manuscript.

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Case Report

EXCLUSIVE TRANSCANAL ENDOSCOPIC REMOVAL OF GLOMUS TYMPANICUM: A STEP-BY-STEP DESCRIPTION OF SURGICAL TECHNIQUE

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ABSTRACT

The purpose of this article is to show step-by-step the exclusive transcanal endoscopic approach to a glomus tympanicum tumour, along with its pre-and post-operative management. Glomus tympanicum is a benign and slow-growing vascular tumour of the middle ear. Staging corresponds to extension within middle ear space and adjacent structures, and it is represented either by Glasscock-Jackson and modified Fisch-Mattox scales. Many strategies have been proposed as treatment options. When surgery is indicated, the evolution of endoscopic ear surgery has allowed an alternative approach to the traditional one. The patient was referred for persistent monolateral pulsatile tinnitus. Computed tomography (CT) scan is essential to define the extension of the lesion in the temporal bone while CT angiography shows its supplying arteries. If the tumour is limited to the middle ear cavity, an exclusive transcanal endoscopic approach is therefore indicated and the patient may be discharged after 24-48 hours after the surgical procedure. Endoscopic excision for small and localized glomus tympanicum tumour represents a safe and effective option with low intra- and post-operative complications.

KEYWORDS: *glomus tympanicum, transcanal endoscopic approach, tumour, middle-ear, endoscopic excision*

INTRODUCTION

Middle ear paraganglioma, also known as glomus tympanicum, is a benign and slow-growing vascular neoplasm arising from the tympanic plexus of Arnold's and Jacobson's nerve onto cochlear promontory (1). It is the most

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common tumour within the tympanic cleft, while is the rarest among its counterparts in other head and neck districts, with the carotid body paraganglioma being the most frequent. All are histologically composed of chief cells and sustentacular cells. Less frequently, a malignant or catecholamine-producing type may be encountered (Fig. 1, 2).

Epidemiologically, glomus tympanicum is more frequent within the female gender, with a bimodal distribution in the late 30s and the early 60s. Clinically a glomus tympanicum often presents with a history of long-term pulsatile tinnitus and auricular fullness, with or without hearing loss (1). Rarely it is associated with bloody otorrhea or neuropathies. In most cases, the diagnosis is incidental. At the otoendoscopic examination, a reddish and bulging tympanic membrane is suggestive of it.

Staging of glomus tympanicum corresponds to the extension within the middle ear space and adjacent structures and it is represented by the Glasscock-Jackson (Table I) and modified Fisch-Mattox scales (Table II) (2). CT- and MRI-scan are very helpful in defining the nature and limits of the lesion while, due to the vascular origin, CT-angiography allows detection of its supplying vascular branches (3).

Therapeutic options may include wait-and-scan policy, external radiotherapy and surgical resection (3, 7). The indications for a conservative approach are non-secreting small tumour (< 1 cm), slow-growing rate, absence of symptoms and older patients with comorbidities precluding major surgery. In these cases, close clinical and radiological follow-up must be planned. External radiotherapy, in terms of conventionally fractionated external beam RT (EBRT) or stereotactic body RT (SBRT), may provide long-term disease control for unresectable growing paragangliomas. Anyway, surgical option is often the preferred method of treatment.

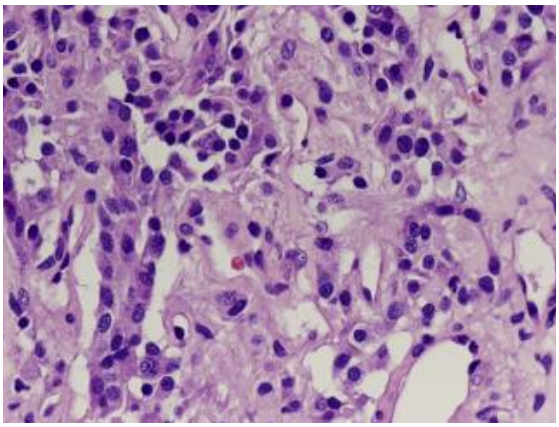

Fig. 1. *High-magnification histopathology of paraganglioma. The chief cells are small with basophilic cytoplasm and have round, granular nuclei (Hematoxylin and Eosin stain).*

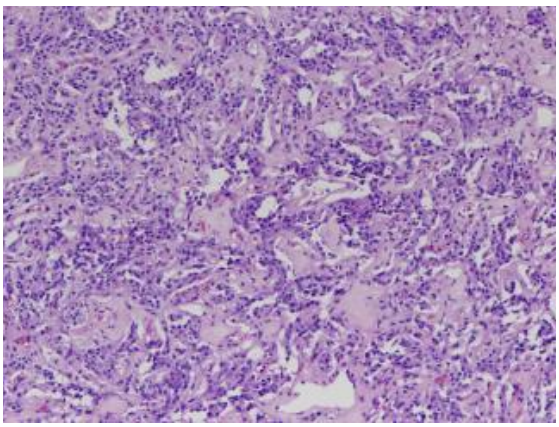

Fig. 2. *Low-magnification histopathology of paraganglioma. The Zellballen architecture is visible, along with a richly vascular stroma and focal fibrosis (Hematoxylin and Eosin stain).*

Table I. *Glasscock-Jackson classification system.*

Grade	Definition
1	Tumor margins completely visible on otoscopy
2	Tumor filling the middle ear
3	Tumor filling the middle ear and the mastoid
4	Tumor extending through the tympanic membrane into the external auditory canal

Table II. *Modified Fisch-Mattox classification system.*

Grade	Definition
A1	Tumor margins completely visible on otoscopy
A2	Tumor margins not completely visible on otoscopy
B1	Tumor filling the middle ear and extending into the hypotympanum or sinus tympani
B2	Tumor filling the middle ear and in the mastoid
B3	Tumor eroding into the carotid canal

Surgical options

Traditionally, most middle ear paragangliomas have been managed with surgical excision and, considering resection, preoperative treatment planning is essential. Firstly, the chosen approach depends on the extent of the tumour within the middle ear and mastoid cavity (1, 2) with the Glasscock-Jackson and modified Fisch-Mattox scales being the most used. Then, the risk of intraoperative blood loss must be estimated: preoperative angiography is mandatory to assess any vessels leading to the lesion, even if in most cases limited to the tympanic cleft embolization is not necessary. Lastly, the need for pharmacological intervention should be considered, to determine whether perioperative a-adrenergic and possibly b-adrenergic blockades are necessary. In this scenario, a transcanal and/or retroauricular microscope-based approach is the traditional technique used to manage this kind of tumour (3-5)..

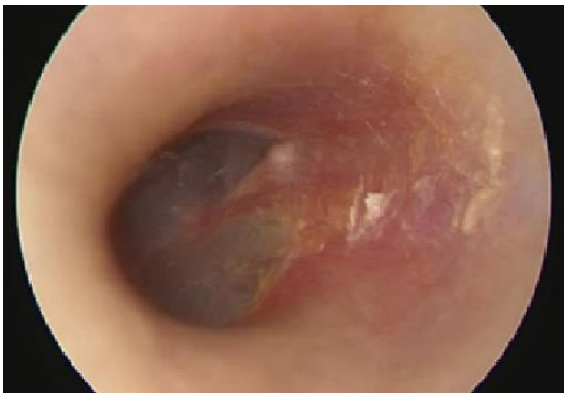

Fig. 3. *Preoperative endoscopic view of left tympanic membrane.*

The transmastoid approach is necessary for tumour extending into the mastoid, into the ear canal or significantly engaging the pro- and hypotympanicum areas. A mastoidectomy is helpful to visualize tumours that extend superiorly into the attic, with an extended posterior tympanotomy in front of tumours extending inferiorly. A modified radical mastoidectomy with or without canal overclosure may be necessary for advanced tumours with external auditory canal erosion. Moreover, even small tumours in patients with very narrow external auditory canal may require postauricular approach. The transcanal microscopic approach is indicated for small tumours limited to the middle ear, even if it is more frequently used in combination with the posterior approach (6, 7).

The rising use of the endoscope in ear surgery introduced a new strategy within the management of this kind of tumour (8, 9, 10). In the beginning, it was just used as a tool to achieve a better visualization of some anatomical details or to explore hidden areas. Then it appeared to be reliable in approaching pathologies of the temporal bone, limited to the middle ear cavity.

Case presentation

A 56-year-old female presented with a history of persistent pulsatile tinnitus limited to the left ear. She did not report any vertigo or other cochleovestibular symptoms. At the otologic examination, the tympanic membrane appeared regular (Fig. 3), while hearing evaluation through pure tone audiometry revealed an ipsilateral air-bone gap of 15 dB (Fig. 4) associated with a type A tympanogram. No stapedial reflex was evocated. A CT scan was then performed, showing a small mass centered in the hypotympanum (Fig. 5A, B) while a CT- angiography showed vascularization from an internal carotid artery vessel in its petrous segment (Fig. 5C). Since the tumour was strictly limited to the pro-/

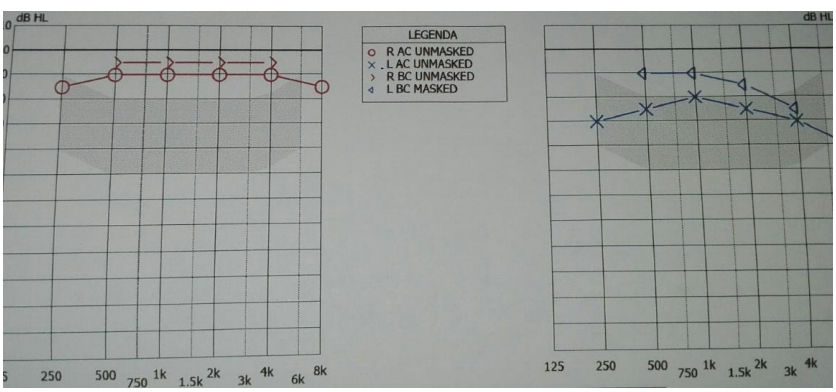

Fig. 4. *Preoperative pure tone audiometry*

hypo-tympanum, it was classified as Modified Fisch-Mattox Class A and as a Glasscock-Jackson Class 1. As previously mentioned, for a small, localized glomus tympanicum tumour a transcanal endoscopic resection was indicated.

SURGICAL TECHNIQUE

Surgical anatomy

The introduction of endoscope in ear surgery allowed a more detailed description of the middle ear anatomy since many subspaces can be easily explored.

Protympanic space

The protympanic area represents the most anterior portion of the middle ear cavity. It communicates superiorly with the anterior epitympanic space, through the tensor fold, and inferiorly with the hypotympanum, while posteriorly it continues into the mesotympanum. Medially, the lateral wall of the vertical carotid artery and the Eustachian tube orifice are found, while laterally it is bounded by the mandibular fossa.

Hypotympanic space

The hypotympanic area represents the most inferior portion of the middle ear cavity. It communicates superiorly with the mesotympanum, to the protympanum through the protiniculus bone ridge and to the retrotympanum through the finiculus bone ridge. It houses the jugular bulb, whose height determines this subsite's volume.

Mesotympanic space

The mesotympanic space is the area one can explore through the external auditory canal. In detail, it is delimitated from the tympanic membrane laterally and the promontory area (the bone covering the cochlea) medially. It contains a malleus handle, the long process of incus, the incudostapedial joint and the stapes superstructure.

Epitympanic space

The epitympanic space is the most superior part of the middle ear cavity, which communicates posteriorly with the mastoid cavity through the antrum and inferiorly with the mesotympanum through the epitympanic diaphragm. Anteriorly the tensor fold is found, superiorly the tegmen tympani (which separates the eardrum from the middle cranial fossa), medially the sovrageniculate fossa and laterally the scutum and the pars flaccida. It can be divided into an anterior and posterior portion by the cog, a bone ridge lying from the tegmen to the cochleariform process, where the tensor tympani muscle is attached.

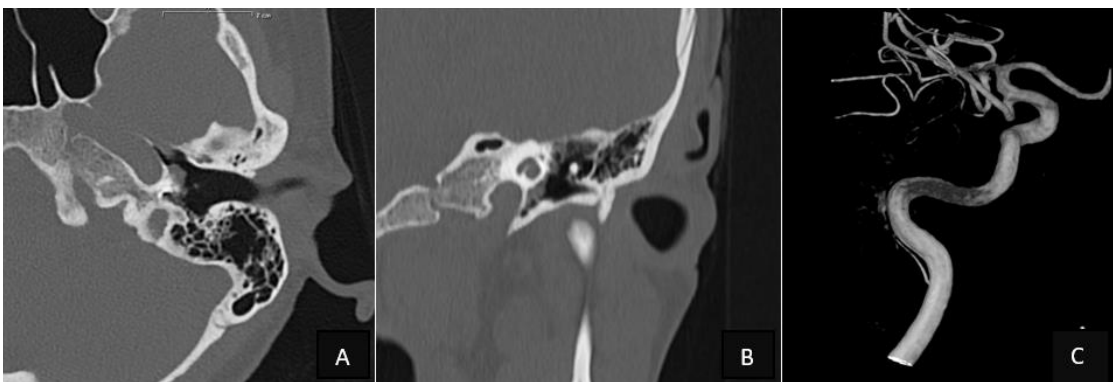

Fig. 5. *Paraganglioma of the left middle ear involving the hypotympanum. A. Axial view of non-contrasted CT-scan; B. Coronal view of non-contrasted CT-scan; C. Preoperative angiography showing a small vessel originating before the petrous segment of ICA.*

This space is occupied mostly by the ossicular chain (head of malleus, body, and short process of incus) and its ligaments, while medially lies the tympanic tract of facial nerve.

Retrotympanic space

The retrotympanic space is the most posterior area of the middle ear cavity. It communicates anteriorly with the mesotympanum and inferiorly with the hypotympanum through the finiculus. It can be divided into a superior and inferior portion by the subiculum bony ridge lying from the round window to the styloid eminence. Moreover, it can be divided into a medial and lateral portion by the tympanic tract of the facial nerve. An important structure is the pyramidal eminence, from which the stapes muscle arises, representing the lateral border of the sinus tympani.

Operating room

The procedure is performed under general anaesthesia with the patient in the supine position and his head extended and turned about 45º toward the opposite side of the involved ear. The video equipment is placed in front of the surgeon and the instruments' trolley and scrub nurse are positioned at the head of the patient. Endoscopes 4 mm in diameter and 18 cm in length, with angulation of 0º and 45º, are used, connected to a high-definition monitor (Karl Storz, Germany) (6). A facial nerve intraoperative monitoring system is carried out using NIM-Response 3.0 (Medtronic Xomed Inc., Jacksonville), with intramuscular electrodes inserted to capture the responses of orbicularis oculi and mentalis muscles.

SURGICAL STEPS

Tympano-meatal flap elevation

The ear is prepared and sterilized by filling the external auditory canal (EAC) with iodine solution. After proper infiltration of EAC skin with mixture of mepivacaine 2% and epinephrine, a posterior incision from the 5 o'clock to the 12 o'clock position is made approximately 0.5/1 cm from the fibrous annulus using a circular scalpel (4, 10). Usually, a previous tattooing of the incision with cautery has been made to help the surgeon to minimize bleeding during this first step (5). A lateral to medial skin dissection is then made detaching the tympanomeatal flap from the underlying bone using cottonoids soaked in epinephrine to avoid excessive bleeding. An otologic microhook usually allows to raise the fibrous annulus and gain access to the middle ear. The tympanomeatal flap is lastly dissected from the malleus and transposed and flattened onto the anterior surface of EAC (Fig. 6).

Tympanic cavity exploration

Once the tympanic cleft and tumoural mass are exposed, the tympanic cavity is explored (10) with both a 0° and 45° endoscope, to assess the extension of the lesion as well as its relationship with the facial nerve and the ossicular chain. Indeed, if the lesion presents with a medial extension relative to the ossicles, chain removal may be necessary to obtain a radical excision of the tumour. However, the well-known endoscopic ability to "look behind the corner" makes this scenario less frequent, as described in the present case.

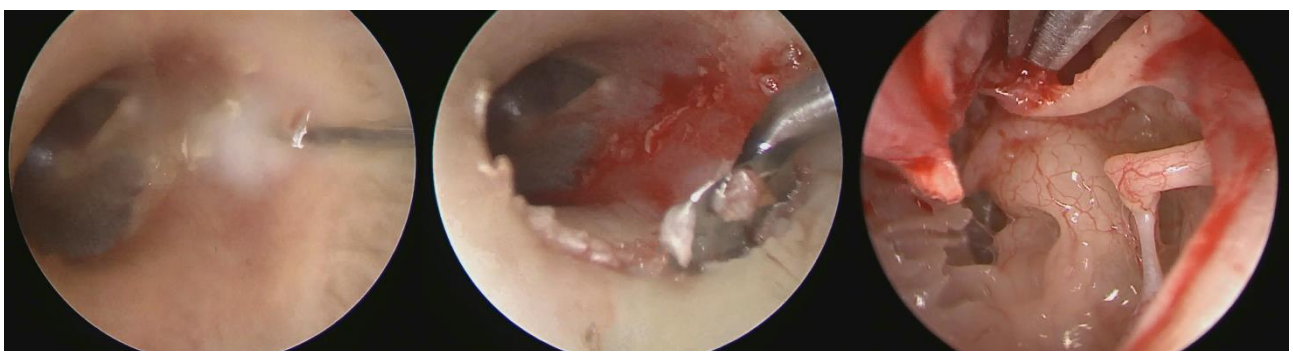

Fig. 6. *Tympanic flap elevation from external auditory canal infiltration to its dissection from malleus handle.*

Tympanic cavity exploration reveals a vascularized lesion consistent with a tympanic glomus type A located at the inferior aspect of the protympanic region bordering with the hypotympanum (Fig. 7). Delicate bone removal of hypotympanic cells is performed utilizing the Piezosurgery to extend the view so that the tumour margins are well visualized. The ossicular chain appeared intact so there was no need to interrupt it. The bone covering the facial nerve did not seem dehiscent and anyway far from the vascular lesion.

Glomus tympanicum cauterization

Cautery of this type of tumour is mandatory before dissection (10). Hence, coarctation of the mass as well as cauterization of blood vessels supplying the tumour is performed using bipolar micro-pliers (Fig. 8).

Tumour dissection and management of eventual bleeding

The dissection is carefully performed with gentle instruments, using a microhook, bone curette and otologic suction (10) (Fig. 9). Cottonoids soaked with saline/diluted epinephrine solution were used to maintain a clean surgical field and achieve adequate hemostasis, which can be refined with bipolar micro-pliers.

Drilling of tumour attachment

Once the mass has been removed, endoscopic exploration must be carefully performed in the tympanic cavity and along the bony margins where the tumour is attached. Deep drilling of the bony tissue underlying tumour bed is absolutely mandatory to obtain a radical surgery (10). This procedure minimizes the risk of recurrence, which is possible in front of tumours arising from paraganglia (Fig. 10).

Revision of haemostasis and closure

At the end of the procedure, further exploration of the tympanic cavity is done to check for possible bleeding spots, which are eventually cauterized with bipolar pliers or cottonoids soaked with diluted epinephrine (Fig. 11). Sometimes, absorbable homeostatic products (e.g., Tabotamp Fibrillar) are left in the surgical field. Moreover, the integrity of the facial nerve through intraoperative nerve stimulation, of the ossicular chain by gentle pressure, and of the tympanic membrane are checked. Lastly, the tympanomeatal flap, eventually repaired with a myringoplasty if damaged, is returned to its original position. No histological examination has been requested due to piecemeal dissection and intraoperative appearance.

Absorbable haemostatic gelatin sponges (Spongostan) are left in the external auditory canal to guarantee proper healing of tympanomeatal flap (10).

Peri- and postoperative assessment

The patient was discharged after 24 hours without complications. An audiometry test was not performed at the discharge as no manipulation

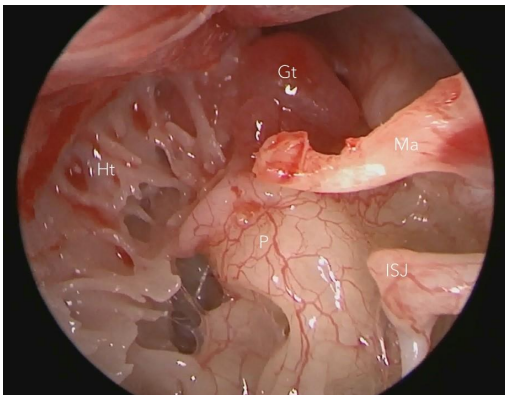

Fig. 7. *Tympanic cavity exploration reveals a vascular lesion consistent with a glomus tympanicum located in the protympanum. Gt: glomus tympanicum; Ma; malleus; ISJ: incudo-stapedial joint; P: promontorium; Ht: hypotympanum.*

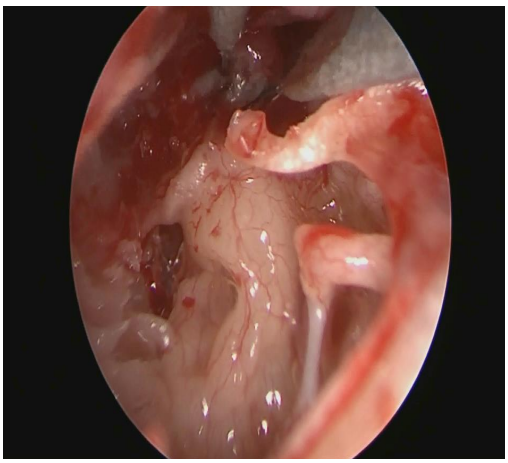

Fig. 8. *Cauterization of glomus tympanicum attachment with bipolar forceps.*

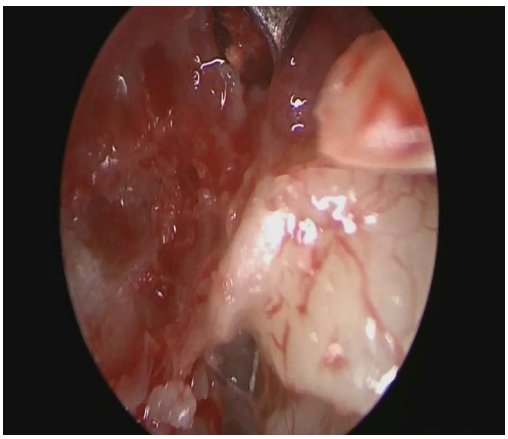

Fig. 9. *Tumor dissection gently performed with the aim of a bone curette.*

of the ossicular chain occurred. The post-operative indications included the usage of antibiotic ear drops and avoidance of water into the treated ear and pressure surges for 1-2 months (11-16). In our clinic regular follow-up is maintained, firstly within 2-4 weeks, then with a post-operative audiometric test after 3-6 months and finally annually through a CT scan. The patient complained of homolateral tinnitus but no vertigo. The audiometric examination at 3 months showed a neurosensorial hearing loss of 15 dB, while a one-year CT scan showed no signs of recurrence.

CONCLUSIONS

Surgical excision for glomus tympanicum is the first treatment choice in most cases. The approach is determined by the location and the extension of the lesion, assessed with CT or MR-scan. In the era of minimally invasive treatments, exclusive endoscopic ear surgery can be considered a valid alternative, especially in Glasscock–Jackson type 1 and modified Fisch-Mattox class A tumours. Indeed, this method provides a dynamic and close tumour visualization, leading to a safe, controlled and effective removal without any sutures or canaloplasty, especially if approached by trained surgeons. Thanks to it, this procedure significantly reduces the operating time, and it is even suitable for 24-hour hospital stay.

Declaration of competing interest

The authors have no conflict of interest to declare.

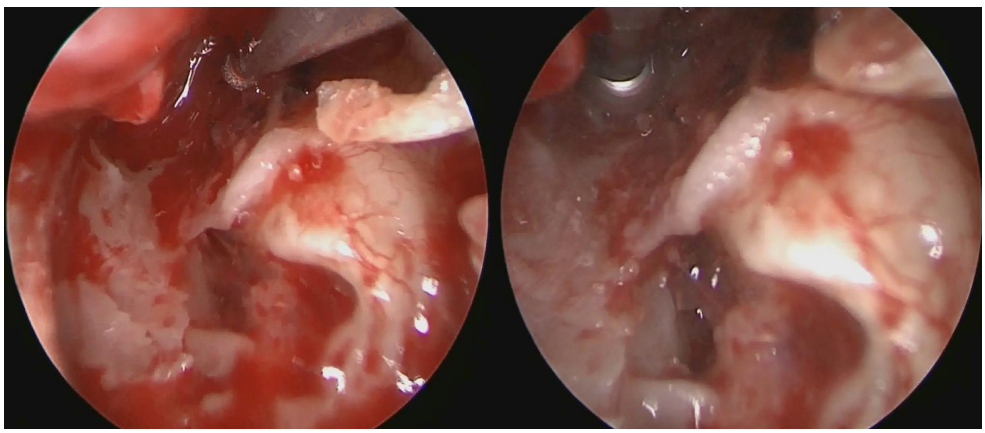

Fig. 10. *Drilling of the protympanic and hypotympanic tumour attachment with the aim of a diamond burr.*

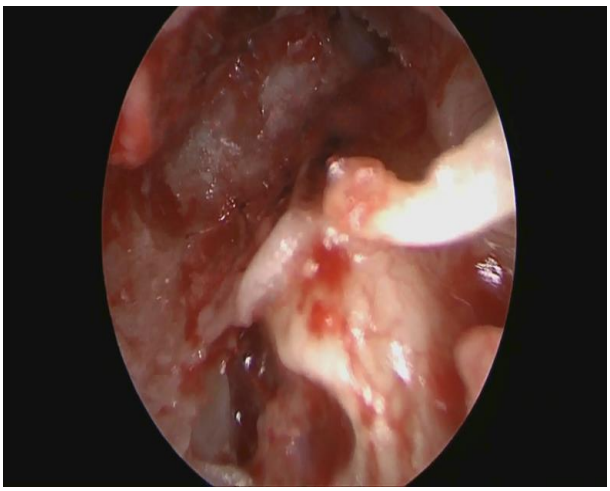

Fig. 11. *Tympanic cavity at the end of surgical procedure of exclusive endoscopic glomus tympanicum excision. The pro- and hypo-tympanic cells are clearly visible as drilled out.*

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Case Report

PERIOSTEUM REVASCULARIZED FLAP FOR RECONSTITUTE OF MANDIBULAR DEFECTS: OUR EXPERIENCE

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ABSTRACT

Mandibular reconstruction is a challenging surgical scenario both for the surgeon from preoperative planning to rehabilitation and for the patient. The biggest challenge for the surgeon is to find the right reconstruction for each patient with a tailor-made approach. Several techniques have been described in the literature, from the use of alloplastic material to the custom-made mandibular prothesis, from the non-vascularized bone grafts to the regional pedicled flaps, and obviously starting at the end of the '80s the vascularized composite free flaps. In the present paper we reported a case of mandibular reconstruction with a free periosteal-fasciocutaneous flap (FPFF) and bone graft, hesitated in a subtotal neo-oxification of the defect, despite removal of the bone graft. A brief review of the dedicated literature is carried out to highlight the options for mandibular reconstruction and the role of periosteum flap in bone regeneration, and its reconstructive potential in head and neck oncological surgery.

KEYWORDS: *periosteum, free flaps, mandible reconstruction*

INTRODUCTION

Several strategies have been described for mandibular reconstruction; from the pedunculated flaps as pectoralis major flap combined with the use of a plaque, to the soft tissue free flap as the anterolateral thigh flap (ALT) with the plaque (1).

However, free vascularized bone-containing free flaps such as fibula flap have become the preferred technique for

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restoration of large mandibular defects, both in adults and children (2). Fibula free flap permitted a complete variety of technique for the insetting of the reconstruction as multiple time described in literature, from the vertical bone distraction (3) to the possibility of bilateral reconstruction of the mandibular body with only one fibula (4). Nowadays the gold standard is not only the bone free flap but we have considered also the chance to use a double free flap in case of a extensive mandibular and soft tissue defects (5). In fact we can find so scheme to understand the best option for the reconstruction take in consideration the dimension and the tissue involved in the defects (6).

There are unfortunately some situations that it's impossible to use free flaps for patient's poor general conditions and comorbidities (e.g., peripheral obliterative arterial disease) contraindicate the possibility of complex bone reconstruction, alternative strategies with acceptable functional results are needed.

We would like to report an emblematic case of a patient with a complex resection for a composite defect after the resection of lower lip extended to the mandibular symphysis, hesitated in an unexpected neo-oxification of the mandible, after reconstruction with free periosteal-fasciocutaneous flap (FPFF) and autogenous bone graft, despite the need to remove the graft. Beyond our surgical technique we performed a review of the literature on the issue is carried out to highlight the osteoregenerative properties of vascularized periosteal flaps.

MATERIALS AND METHODS

A 78-year-old patient was referred to our attention for relapsing squamous cell carcinoma (SCC) of the lower lip. He had undergone, as first treatment, surgical resection and radiation therapy (RT) on T site and neck. After work-up the tumour was staged as yrpT4aN0M0 SCC G2, with involvement of lower lip in toto, the skin of the chin, and mandibular symphysis.

The situation would require an ideal reconstruction with double free flap, fibula for mandibular restoration and a forearm or an antero-lateral thigh for soft tissues and skin filling but poor general conditions contraindicated such demanding procedure with an elevated risk of failure (5, 6). Therefore, we planned a reconstruction with forearm FPFF. with bone graft (autogenous frozen mandible graft) to be able to reconstruct the soft tissue defects and try to give a better reconstruction for the mandibular defects than the single plaque. The resection includes the entire lip and is extended for 5 cm to the skin of the chin in block with soft tissue and mandibular symphysis, for a stretch of 8 cm from the left incisor to the right canine. Intraoperatively the resection margins appeared macroscopically free. Extemporaneous biopsies were performed to be sure of the results and these were negative.

After a positive Allen test performed on both forearm, we chose the left one that was the non dominant hand for the donor side. The forearm FPFF was harvested with blunt dissection of 10x8cm fasciocutaneous paddle including the palmaris longus tendon by the radial side to fully restore lower lip and the skin of chin. The periosteal flap, with a maximum size of 12x5cm, was gently dissected avoiding its dissociation from the radial pedicle at the insertions of brachioradial muscles, cranially, and the radial flexor of the carpus, distally. An autogenous frozen demineralized graft was then obtained by immerging the resected mandibular segment in liquid nitrogen (-196°C) for 10 minutes for a couple of times with a 20 minutes'

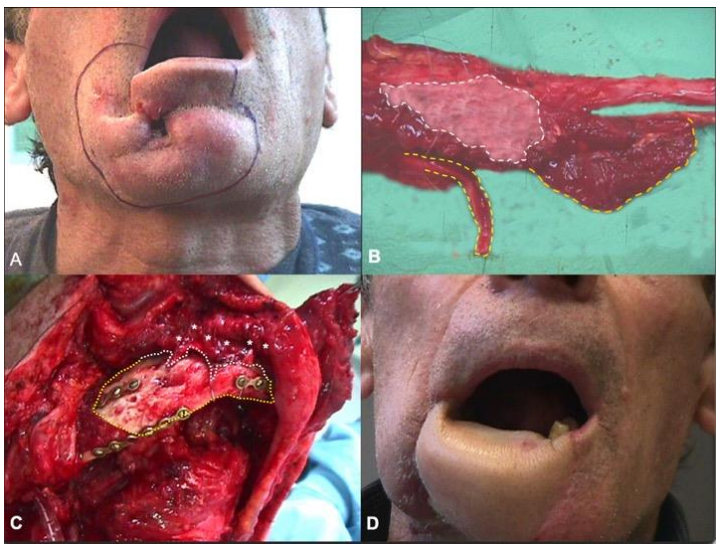

Fig. 1. *A): Pre-operative picture shows the relapsing tumor of the lower lip involving skin of the chin; B): Intraoperative picture of the FPFF shows the periosteal paddle (white dotted line), the tendon of palmaris longus muscle (yellow dotted line) and the flexor carpi radialis muscle (orange dotted line); C): Intraoperative photo showing the fixed freeze-treated mandible covered over the inner surface by the periosteal paddle of the FPFF (* and white dotted line). The lateral and inferior portion of the symphysis was not enveloped by periostium (yellow dotted line); D): Post-operative result 1 month after surgery.*

interval and then repositioned in place. The tendon of palmaris longus muscle was positioned along the profile of the lip to recreate it, sutured with the maxillary periosteum at the level of nasolabial fold bilaterally. The periosteal paddle was stretched along the outer surface of the frozen autogenous demineralized mandible, leaving an exposed bone surface for 1 cm in the left lateral portion (Fig. 1).

RESULTS

Surgery was radical and no immediate post-operative complications were observed. Unfortunately, after 1 month a local infection resulted in bone cutaneous exposure of 1 cm with chronic osteitis where the bone graft was not covered by periosteum, and therefore 4 months later become necessary to remove entirely the bone scaffold. Surprisingly, newly formed bone was generated in correspondence with the periosteal surface, thus determining the tightness of the mandibular arch (Fig. 2). The patient died of cardiovascular disease 12 months after the surgical procedure.

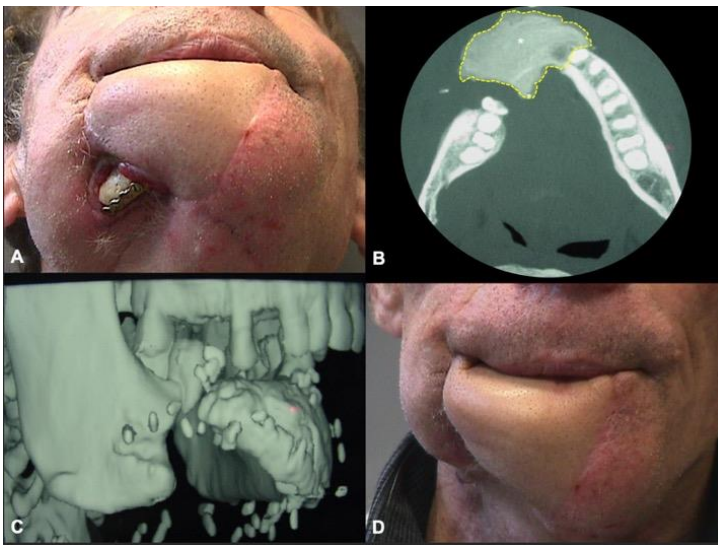

Fig. 2. ***A):*** *Bone graft exposure 6 months after surgery. The graft is exposed in the area not covered by periosteum paddle;* ***B):*** *CT scan of the mandible performed after revision surgery for bone graft removal. A large amount of regenerated bone is evident;* ***C):*** *CT 3D-reconstruction shows multiple areas of neo-ossifications;* ***D):*** *Morphologic result after revision surgery: the profile of the mandibular arch has not been significantly changed after bone graft removal.*

DISCUSSION

Periosteal free flaps are something not new in the literature. Indeed, initially this option was proposed by Kelley et al. in 2003 for the optimization of vascularization of maxillary bone grafts (7), and by Roselli et al., Calabrese et al., Cantù et al., associated with autologous frozen bone as surgical option for oncological mandibulectomy (8-10). Subsequently there have been only few reports. A single case experience was described in 2018 by Sierra et al: the authors used a bone allograft segment covered with a re-vascularized fibula periosteal flap in an 11-year-old patient submitted to mandibular resection for Ewing sarcoma (11). Allograft came from a cadaver tissue bank. Bettoni and coll. reported their experiences in managing osteoradionecrosis of the mandible with forearm FPFF, showing acceptable results in patients without weakened mandibular arch (12, 13). Interestingly, the authors systematized the forearm FPFF harvesting technique and evidenced the advantages of a FPFF compared to pure periosteal free flap, especially for filling soft tissues, and monitoring the flap. Öhman et al. assessed whether customized titanium, hydroxyapatite bioceramic coated patient specific implants associated with soft tissues flaps, can significantly contribute to reconstructing large mandibular defects. It is important to underline that reconstruction was not homogeneously carried out with periosteal re-vascularized flaps in the series, but also with direct closure, or even pectoralis major flaps (14).

In all these studies authors reported a high failure rate, firstly related to rejection of the scaffold: those is consistent with our case, but our result led us to a broader thinking. Indeed, despite the need to remove the scaffold, the FPFF was able to regenerate a large amount of new bone, sufficient to replace the missing mandible arch with areas of pseudoarthrosis laterally where not covered by periosteal flap. The case confirmed that periosteal flap has extensive osteoregenerative-osteoinductive properties. This hypothesis was already formulated by several authors who demonstrated that periosteum-preserving surgery could lead to newly bone formation both in dental practice during augmentation surgery, and in mandibular resection (15-22). Moreover, in some studies on animal model, vascularized periosteal flap were demonstrated to be able to regenerate vascularized functional bone, if integrated with a proper allograft demineralized bone matrix, acting as an *in vivo* bioreactor (15-17). The *in vivo* bioreactor is a vascular territory as well as a regenerative niche for vascularization and remodelling of bone grafts. Huang et al., described the use of rabbit skull periosteal flap pedicled on

supraorbital artery as bioreactor, highlighting the advantages compared to the use of other tissues such as muscles (21). According to the authors, periosteum is an ideal niche with skeletal progenitor/stem cells, abundance of molecular signals, and increased nutrient-rich blood supply. Moreover, it acts as a natural barrier membrane to prevent soft tissue invasion.

CONCLUSIONS

The present case showed the high neo-oxification potential of FPFF. It should be applicable not only in selected cases, with unfavourable general conditions that contraindicate a free flap containing bone, but can also become a viable alternative in the reconstruction of complex defects where the use of double flaps would be indicated because it could be effective, timesaving and with less morbidities to the donor site and a lower risk of failure of the reconstruction (6).

In our opinion, larger studies are needed to produce increasingly sophisticated scaffolds, adequate to guide correctly the neo-oxification that permitted a different solution for the mandibular reconstruction from the use of fibula free flap. Fibular free flap still remains the first option for the mandibular reconstruction as multiple time described in literature (23).

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Case Report

SEPTIC THROMBOPHLEBITIS OF INTERNAL JUGULAR VEIN AND PULMONARY EMBOLISM: LEMIERRE'S SYNDROME, A FORGOTTEN BUT PRESENT LIFE-THREATENING COMPLICATION OF ACUTE PHARYNGO-TONSILLITIS

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ABSTRACT

Lemierre's Syndrome is characterized by clinical or radiological evidence of suppurative thrombophlebitis of the internal jugular vein with a history of recent oropharyngeal infection and can be complicated by septic systemic embolism. The disease is usually caused by Gram-negative anaerobic organisms, mainly *Fusobacterium necrophorum*. Once called the forgotten disease in the pre antibiotics era, it may not be that uncommon after all. We report a case of Lemierre's Syndrome in a 14-year-old patient, with a blank medical history, with an oropharyngeal infection and onset of neck and thoracic pain. Computed tomography of the neck and thorax showed a thrombophlebitis of the internal jugular vein and septic emboli in the lungs. *F. necrophorum* was isolated from blood cultures. The isolated *F. necrophorum* showed susceptibility to metronidazole, clindamycin and betalactam/ beta-lactamase inhibitor combinations with no signs of resistance or reduced sensitivity, so prolonged multidrug therapy was considered the mainstay of treatment. Anticoagulation is believed to play a favourable role in the recovery of the disease because of the potential for faster resolution of thrombophlebitis, but the use of anticoagulation is still heavily debated due to conflicting results in literature. Lemierre's Syndrome is an unfamiliar syndrome, once considered rare, with an increasing number of reported cases recently. It is due to septic complications of oropharyngeal infections, which lead to thrombophlebitis of the internal jugular vein with potentially fatal complications occurring primarily in young, otherwise healthy individuals, which requires a prompt diagnosis and treatment. In this case report, we present a case of Lemierre's Syndrome in a 14-year- old

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patient treated with long-term antibiotic and anticoagulant therapy, considering the young age and the extent of the septic emboli to lungs, with complete resolution of the disease at the end of the treatment.

KEYWORDS: *Lemierre's Syndrome, thrombophelebitis, internal jugular vein, septic emboli, case report*

INTRODUCTION

In 1936 André-Alfred Lemierre reported on a series of 20 cases of postpharyngitis sepsis, of whom only 2 survived. The syndrome, diagnosed by a combination of clinical signs, positive blood cultures and radiological findings, classically comprises pharyngeal infection, internal jugular vein septic thrombosis, producing disseminated emboli to the periphery (often septic pulmonary emboli) and the presence of the anaerobic bacterium *Fusobacterium necrophorum* in blood culture (1, 2). This condition was eventually named after Lemierre's syndrome.

Lemierre's Syndrome usually begins as a local oropharyngeal infection and presents with fever, cough, sore throat and neck swelling. Later during the course, after the throat had settled, infection spreads via blood stream to other organs (the venous thrombosis is likely the result of endothelial dysfunction caused by inflammatory factors from the local infection) and led to overwhelming systemic infection (3). Lemierre recognized the importance of the progression from thrombophlebitis of the tonsillar veins to internal jugular vein thrombophlebitis with subsequent septicemia due to the release of small pieces of infected thrombus (4). This spread of septic emboli may produce lung lesions (lungs are affected in up to 85% of cases) that commonly appear as necrotic cavitary lesions but can also present as infiltrates, pleural effusions, empyema, lung abscesses, and necrotizing mediastinitis and patients can develop acute respiratory distress syndrome that requires mechanical ventilation (5, 6). Less commonly the hematogenous spread may involve joints, liver, spleen, kidneys and muscles (7).

Several authors highlighted that septic thrombophlebitis was also a feature of *F. necrophorum* infection in other sites, such as otogenic infection, having a higher incidence of intracranial complications, iliac vein thrombophlebitis associated with post-prostatectomy infection, portal vein thrombophlebitis associated with infection secondary to rectal carcinoma, and mesenteric thrombophlebitis after an appendectomy. Stimulating clot formation and multiplying in the clot with subsequent embolic spread is clearly a fundamental feature of the pathogenesis of *F. necrophorum* infection (8,9).

Although uncommon, clinicians need to be aware of this condition because patients with Lemierre's Syndrome require prompt and appropriate therapy.

CASE REPORT

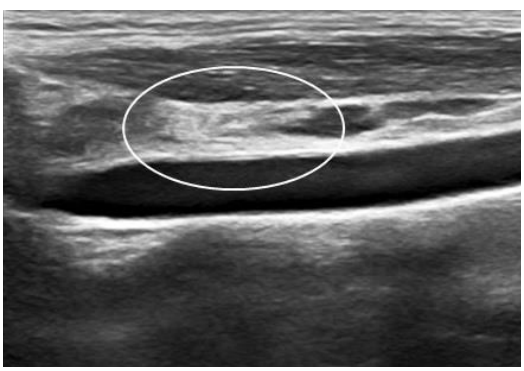

Fig. 1. *Neck ultrasound showed venous blockage in the internal jugular vein by a thrombus (circle).*

We describe the case of a fourteen-year-old female patient who accessed the ER because of sore throat, fever and chest pain. Her clinical history was silent. She has presented a sore throat for four days and a fever for three days with peaks up to 40°C. She was therefore taken to her general medicine practitioner, who prescribed her an oral antibiotic with clarithromycin for pultaceous tonsillitis. After one day without improvement, her doctor advised her to switch to a therapy with amoxicillin-clavulanate, with an improvement in her symptoms. The same night, however, she woke up with chest pain localized on the right shoulder and in the scapular region bilaterally, which worsened with deep inspiration and was only mildly responsive to ibuprofen. For this reason, she accessed an ER in a peripheral hospital, where a nasal- pharyngeal swab for Sars-cov-2 (negative) and blood samples (mild increase in inflammation markers, CRP 69 mg/L, WBC 13.360/mmc) were performed. ECG and chest X-Ray were unremarkable.

At the ENT evaluation, hypertrophy and medialization of the left tonsil with a laterocervical lymphadenopathy was diagnosed. The patient was therefore admitted in the Paediatric ward to start endovenous administration of amoxicillin-clavulanate, which the next day was changed to ceftriaxone. A bedside ultrasound showed multiple reactive lymphnodes in

the left laterocervical region and the nasal-pharyngeal swab culture revealed no pathological microorganism growth. The day after a new US was then performed, which confirmed the presence of left lymphadenopathy but also showed a poorly compressible left internal jugular vein, suggesting a jugular vein thrombosis (Fig.1).

In light of all these findings a diagnosis of Lemierre's Syndrome was suggested, which was confirmed by an urgent neck CT scan which showed thrombophlebitis of the left internal jugular vein, multiple ovalar lymphnodes in the left laterocervical region, at the mandibular angle and in the sovraclavear compartment bilaterally (Fig. 2). Lung CT scan was also performed and showed bilateral cavitated pulmonary nodules, as result of metastatic septic emboli (Fig. 3).

The patient was therefore transferred the University Hospital of Verona and admitted in the Paediatric ward under the ENT team care. She was administered an anticoagulant therapy with Enoxaparin at the therapeutic range of 5000UI. The antibiotic therapy was set with ceftriaxone 2g/die and clindamycin 600g/die, substituted the next day according to the infective disease consult with metronidazole 500 mg x3/die. After ten days of antibiotic and anticoagulant therapy, symptoms and inflammation markers were back to normal. The neck US showed patency of the left internal jugular vein.

The patient was discharged with a prescription of Enoxaparin for three months and oral amoxicillin-clavulanate 1g x 3/die for a month, until the follow-up CT scan programmed after one month. This confirmed patency of the vein and showed that the pulmonary nodules were diminishing in number and size (Fig. 4). The patient's conditions were evaluated every month for 6 months both clinically and with blood tests. A tonsillectomy was also scheduled in order to prevent the recurrence of the condition.

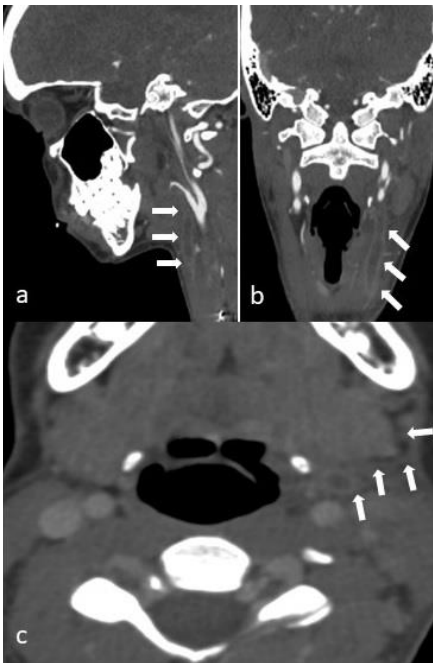

Fig. 2. *Contrast-enhanced CT of the neck region with axial, coronal and sagittal reconstruction showing a hypoechoic thrombus in the middle and distal tract.*

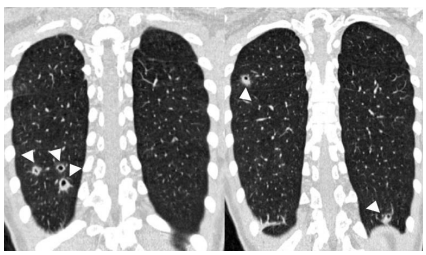

Fig. 3. *Chest computed tomography (CT) with coronal reconstruction (A and B) demonstrating multiple bilateral pulmonary nodules, most of which were cavited and associated with areas of consolidation (arrows).*

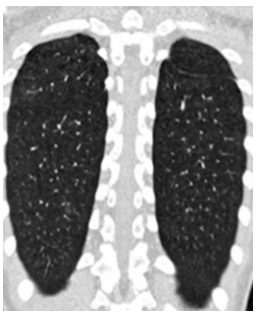

Fig. 4. *After 4 weeks of treatment, repetition of chest CT scan showed resolution of pulmonary localisations.*

DISCUSSION

Lemierre's Syndrome is an uncommon disease of the postantibiotic era but can carry dangerous potential sequelae with a high mortality rate. In the past the syndrome was common, but with the widespread use of antibiotics for upper respiratory tract infection in the 1940s, the incidence of the syndrome dropped, and it eventually became known as the "forgotten disease" (10). Since the 1990s, however, there has been a marked resurgence of Lemierre's syndrome, and it is unclear if this rising trend in cases is due to advancement in diagnostic techniques, restriction in antibiotic use for sore throat, decreased number of tonsillectomies or increased antibiotic resistance to organisms. It is usually seen among young adults, with the highest incidence between 15-25 years of age, and according to a Danish study made by analysing all the cases from 1998 to 2001, the annual incidence among individuals aged 14 to 24 was 14.4 cases per million people while the incidence in the whole population was 3.6 cases per million people (11).

Little is known regarding the reason for this age distribution with possible reasons linked to anatomy, hormonal changes, social behavior (human to human oral contact), co-infections and the presence of tonsils (reaching their largest size in puberty) (12). Lemierre's Syndrome refers to septic

thrombophlebitis of the internal jugular vein (IJV) and despite its nonnegligible annual incidence of > 1/ 100000, often goes undiagnosed due to its non-specific symptoms (13). The syndrome typically begins with an oropharyngeal infection, usually in association with tonsil or peritonsillar involvement. Other antecedent conditions include oral cavity or dental infections, mastoiditis, otitis or infectious mononucleosis (14). Lemierre's Syndrome is caused by bacteria that invade the pharyngeal mucosa and lateral pharyngeal space, inflammation within the wall of the vein and infected thrombus within the lumen resulting in subsequent internal jugular vein septic thrombophlebitis and metastatic infections, due to disseminated emboli to the periphery (often septic pulmonary emboli) (15,16).

The most commonly associated organism, *F. necrophorum*, is a gram-negative, anaerobic bacterium that is part of the normal flora of the oropharynx, but the recent development of various antibiotics and advancements in medical care have led to diversified and antibiotic-resistant strains, therefore multiple other bacteria have been implicated in Lemierre's Syndrome, such as S*treptococcal species*, *Eikenella corrodens*, and *Staphylococcus aureus* (17).

A multidisciplinary approach is necessary to treat patients with Lemierre's Syndrome. Collaboration with infectious disease experts, radiologists and otolaryngologists is essential to reach a prompt diagnosis and achieve a good therapeutic outcome, in order to prevent its devastating effects (18).

Antibiotic therapy is the mainstay of treatment. *F. necrophorum* shows *in vitro* susceptibility to metronidazole, clindamycin, beta-lactam and carbapenems. Any antimicrobial regimen should include a b-lactamase inhibitor, because b-lactamase-producing strains of F. necrophorum have been reported and co-infecting pathogens might also produce b-lactamases (19). One review showed that metronidazole was the most commonly prescribed antibiotic; it shows excellent penetration into most tissues and can be administered orally without compromising bioavailability.

In vitro data have shown that metronidazole or carbapenem shows greater bactericidal activity against F. necrophorum than clindamycin (20). F. necrophorum is intrinsically resistant to macrolides, fluoroquinolones, tetracyclines, and aminoglycosides (22,21). A review of 100 F. necrophorum isolates from 1990 to 2000 revealed that all strains were susceptible to metronidazole, clindamycin, imipenem, amoxicillin-clavulanate, and cefoxitin and 15% of strains were resistant to erythromycin. The level of 15% resistance to erythromycin may be important as this drug or its newer derivatives are regularly prescribed by primary care physicians for the treatment of upper respiratory tract infections (20-22). Antimicrobial therapy should be prescribed for 3-6 weeks. Once the infection is controlled, therapy can be completed orally.

Despite providing appropriate antimicrobial treatment, the observed clinical response might be slow. One explanation for the slow response is that Lemierre's Syndrome is an endovascular infection and that antibiotics have difficulty in penetrating the fibrin clot (23, 24). Theoretically, a septic thrombus sequesters bacteria and creates a barrier to antibiotic penetration. When the thrombus is dissolved by anticoagulants, the bacteria are exposed to a higher concentration of antibiotics, increasing accessibility (20, 23, 24).

On the other hand, the role of anticoagulation in the treatment of Lemierre's Syndrome is more uncertain and it is not clear its effect on the recanalization of the vessels. Due to a lack of high-level evidence there is no current consensus

(25). Some physicians believe that it is possible to achieve the dissolution of the thrombus simply by using antibiotics, since it originated from an infection. Other physicians instead confirm that anticoagulation plays a favourable role in the recovery of the disease because of the potential faster resolution of thrombophlebitis and the prevention from other complications, such as cavernous sinus thrombosis or pulmonary embolism (13). Theoretically speaking, behind these two opposite ideas, there is the thought that, given that the thrombus sequesters bacteria, with anticoagulants there is the risk of increasing the bacteraemia and of causing more septic emboli, but on the other hand it is also possible to increase the effect of the antibiotics (13).

Many studies or reviews indicate a favourable outcome both with and without anticoagulation. Despite this, there is an increase in use of anticoagulant in treatment of Lemierre's Syndrome over the last few years. In older reviews 21-23% of patients were given anticoagulants (26, 27) in contrast to the reviewed population of Johannesen et al. and Rebelo et al. (64% and 100% resp.) (26, 28).

A recent meta-analysis examined 394 patients treated for Lemierre's Syndrome between 1980 and 2017 but failed to find a statistically significant improvement in vessel recanalization and mortality using anticoagulants (25). Many recent cases, especially considering the pediatric population, reported the use of some form of anticoagulants which seemed to have reduced or slowed the progression of thrombosis (29). The use of anticoagulants is still questionable and randomized

clinical trials should be set in order to identify the optimal anticoagulant therapy.

Even the duration of the anticoagulation is debated, but it is probable that it is indicated for at least six weeks due to the concomitant embolic disease (30, 31). For example, Goldenberg et al have analyzed the outcome of 8 patients treated with anticoagulants for a median duration of 3 months (range: 7 weeks-1 year) noticing the complete recovery from the disease and no recurrent thromboembolism or anticoagulant-associated major hemorrhage after one year of follow up (32).

Therefore, the treatment should be tailored for every patient considering his clinical status, the kind of disease complications and the improvement obtained from the therapy. This is why an adequate follow up should be set, providing US of the neck or CT scans to monitor the recanalization of the internal jugular vein and regular blood tests to analize the inflammatory markers. In the literature there is no consensus on how long the follow up should be and on how often the clinical evaluations should be organized. However, it seems common to repeat the imaging after one or two months and to monitor the patients for no more than six months or one year.

Finally, surgical treatment of the thrombosis is very seldomly indicated and the internal jugular ligation or excision is rarely performed. The main function of surgery is to drain the cervical abscess, commonly in the peritonsillar and lateral pharyngeal region, and to treat possible complications such as lung empyema or septic joints (29).

CONCLUSIONS

Lemierre's Syndrome is now a rare entity which can be fatal. It is a bacterial condition, mostly caused by Fusobacterium necrophorum, with systemic complications which can be fatal, and it should be suspected in young people with persistent fever and neck pain and/or distal metastatic septic lesions. Contrast-enhanced computed tomography of the neck is the best diagnostic method as it detects vascular thrombosis of the internal jugular vein and other complications such as pulmonary emboli. A multidisciplinary approach is necessary to treat patients with Lemierre's Syndrome. Collaboration with infectious disease experts, radiologists and otolaryngologists is essential to reach a prompt diagnosis and achieve a good therapeutic outcome, in order to prevent its serious long-term complications, including neurologic deficits and debilitating conditions potentially requiring long and resource-intensive additional care.

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Case Report

USE OF DERMAL FILLERS TO TREAT ANGULAR CHEILITIS. A CASE REPORT

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ABSTRACT

Angular cheilitis is a common perioral pathology that usually presents with erythema, fissures and crusts accompanied by pain and/or itchiness. Angular cheilitis causes, in addition to blemishes, a functional limitation in motility and oral expression. We present the case of an elderly patient treated with dermal fillers which solved his pathology.

KEYWORDS*: angular cheilitis, dermal filler, hyaluronic acids, perioral pathology*

INTRODUCTION

Angular cheilitis is a relatively common perioral pathology that can affect one or both sides of the mouth. It is characterized by erythema, fissures and crusts accompanied by pain and/or itchiness. Incidence is variable between 0,7 and 3.8% in the general population, but it is higher in certain subpopulations like elderly people (1, 2). Moreover, hospitalized elderly people and denture wearers seem to have an even higher incidence as reported by Peltola et al. (3). This pathology can affect facial aesthetics by causing scarring of soft tissue surrounding the mouth and impairing facial mimic. The purpose of the present study is to review treatment options for angular cheilitis and present a patient treated by injection of dermal fillers.

CASE REPORT

A male patient aged 77 presented to our dental clinic with a history of recurrent angular cheilitis. Another dental

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specialist had already made the diagnosis and attempted treatment before. The cause was thought to be drooling of saliva due to a reduced vertical occlusal dimension, therefore the administered treatment was occlusal vertical augmentation using multiple dental reconstructions. However, after treatment, the patient reported no improvements, he was then referred to our clinic.

The patient reported no relevant active pathology at the time of the visit. Intraoral examination revealed good dentition, class I occlusion and multiple tooth reconstruction. Although dental reconstruction was correctly performed there was still a slightly decreased vertical dimension. There was also a slight lip incompetence, but it did not affect the function of the stomatognathic system. No signs and/or symptoms of stomatitis were present at the time of the visit (Fig. 1).

Since the angular cheilitis was likely caused by a combination of lip incompetence and reduced vertical dimension, following reports of success in using hyaluronic acid fillers (4) to treat angular cheilitis, the patient was offered a treatment with Teoxan Rha3 (Teoxane SA, Rue de Lyon, 105 Geneve, CH) to improve lip competence. The patient was informed that dermal fillers might have been a solution though requiring more than one treatment to obtain result. In any case the patient was requested to undergo periodical re-evaluation and re-treatment if necessary, as dermal fillers are known to resorb over time (5).

Informed consent was obtained, and the patient underwent the treatment with a 25G cannula, inserted in the subcutaneous area, and 0.5 ml of dermal filler per side was injected.

The patient was asked to be re-evaluated at 2 weeks and 4 months after injective treatment. The results were satisfying and there was no sign of residual angular cheilitis; additionally, the patient reported an improvement in facial aesthetics. At 4 months the patient was recommended another treatment to maintain the results, he accepted and he is currently in follow-up (Fig. 2).

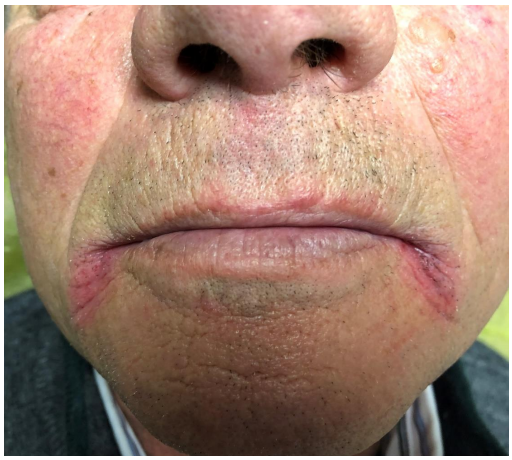

Fig. 1. *Patient presenting angular cheilitis before treatment.*

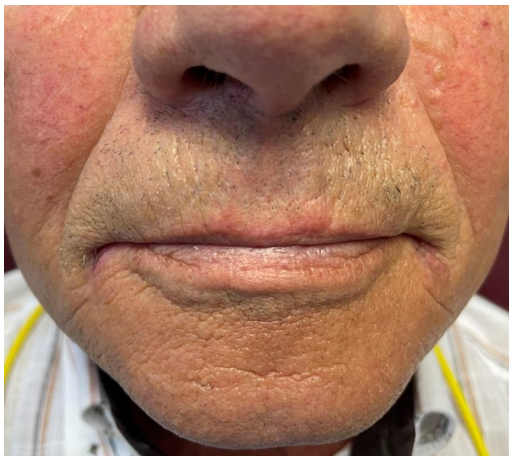

Fig. 2. *Patient at 4 months after treatment with no sign of angular cheilitis.*

DISCUSSION

Angular cheilitis (AC) has different etiologies, but it is mainly caused by infection, irritation and allergies. Oral flora plays an important role, the main species involved in AC pathogenesis are *S. Aureus* and/or beta-hemolytic streptococci.

Bacterial infection is often accompanied by an overgrowth of *C. Albicans* (1, 2). AC can be confused with another relatively frequent pathology, which in the post-acute phase has a similar clinical presentation: herpes simplex.

However, anamnesis and clinical examination in the early stages of the disease allows correct differential diagnosis. Other less-frequent pathologies, which can have a similar clinical profile are impetigo, pemphigus vulgaris, oral syphilis and labial tuberculosis.

Risk factors for the development of AC can be divided into systemic and local. Local risk factors include saliva quantity and/or quality, mouth breathing, overclosure of the mouth, lip-licking habit, drooling, poor oral hygiene, loss of vertical dimension, and use of local medications (corticosteroids or antibiotics). Among systemic factors are age (childhood and old age are more affected), altered hormonal status (pregnancy, hypothyroidism, hyperthyroidism) nutritional deficit (iron, folate, group B vitamin deficit), systemic drugs, autoimmune disease [systemic lupus erythematosus (SLE), Sjogren's and inflammatory bowel disease (IBD)], radiation-induced mucositis and immunodeficiencies (genetic, acquired or iatrogenic).

AC has a higher prevalence in elderly people because of facial ageing and reduced vertical dimension. The latter is

relatively common in old age; it can be caused by edentulism, dental attrition, worn-down dentures and/or maxillary atrophy. Moreover, older people tend to have a weaker immune system and have a higher prevalence of nutrient deficiencies. All these factors contribute to a higher prevalence of AC.

Since AC can have multiple etiologies and it can be difficult to identify the correct treatment for each patient, therefore a multidisciplinary approach is often required. Common topic treatments for this pathology are barrier creams, antifungals, antibiotics and local corticosteroids depending on the etiology. Other general treatment includes nutritional supplements, improving oral hygiene, avoidance of irritants and restoration of occlusal vertical dimension. However, it must be taken into account that augmentation of the occlusal vertical dimension has an anatomical limit. Morever, augmentation of the vertical dimension can affect the masticatory pattern which is difficult to modify and can generate discomfort in the patient. In cases requiring systemic treatment by oral antibiotics or antifungals, special attention must be paid to drug interactions.

Elderly people tend to have multiple comorbidities and therefore are in treatment with multiple drugs which can have interactions with antibiotics or antifungals; this is especially important in the case of oral anticoagulants. Some forms of angular cheilitis are difficult to treat, due to contraindications to antibiotics/antifungals or are refractory to treatment. In these cases, the use of facial dermal filler should be considered as a way to improve lip volume and/or reduce skin laxity. Moreover, it is proven that dermal fillers improve hydration of the skin etc. and therefore they should improve symptoms of AC as a treatment per se (6).

Dermal fillers are a widely used treatment for facial rejuvenation, but possible applications are not limited to facial aesthetics. Dermal fillers are not devoid of complications, and they have a series of contraindications that must be taken into account. Dermal fillers have very few reported drug interactions, moreover, they are usually well-tolerated and do not require daily treatment. Absolute contraindications for dermal fillers are folliculitis, furunculosis, previous infiltrations with non-resorbable material, autoimmune diseases, immunosuppression, and allergy to components. Relative contraindications are gestation, oral anticoagulant treatment, history of keloid scars and uncontrolled diabetes. The majority of adverse reactions are mild and transient (ecchymosis, erythema, pruritus, oedema), but serious adverse reactions such as paraesthesia, necrosis, granulomatosis and blindness are reported (7-9). Most of these side effects can be avoided by proper planning, but they can also happen to experienced clinicians. Complications can be treated with laser therapy, hyaluronidase injection or surgical excision depending on the type and extension of the complication (7-9).

It is important to communicate these complications to the patient and to make sure that they are understood. Moreover, the practitioner must be well-trained and should have a detailed knowledge of facial anatomy.

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Case Report

ENDOSCOPIC ASSISTED TRANSCERVICAL-TRANSPAROTID APPROACH FOR PARAPHARYNGEAL GIANT TUMOR: A CASE REPORT.

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ABSTRACT

Parapharyngeal space (PPS) is an anatomical complex area of the neck that extends from the skull base to the hyoid bone level. Tumors arising from this space are a heterogeneous group of neoplasm, indeed more than 70 different histological types have been described. This is a case report of a 48-year-old man with a giant tumor of PPS. It has been removed using a transcervical-transparotid route. The use of the endoscope helped the surgeon to reach the deepest and highest part of the PPS, identify a residual of tumor and remove it. The endoscope should be considered a crucial part of the surgical armamentarium in the approach of PPS masses in some cases. In fact, it assists the surgeon on thoroughly examining the PPS in all its extension. Furthermore, the endoscope in this case avoided other and more invasive approaches, reducing associated comorbidities.

INTRODUCTION

Parapharyngeal space (PPS) is an anatomical complex area of the neck that extends from the skull base to the hyoid bone level. Tumors arising from this space are a heterogeneous group of neoplasm, indeed more than 70 different histological types have been described. They represent 0,5% of the head and neck neoplasms: 82% of them are benign tumors, 18% are malignant (1). The most frequent tumors arise from salivary gland (45%) and nerves (41%), but also rare neoplasms are described such as teratomas, cystic hygromas, rhabdomyosarcomas or chondrosarcomas (2).

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Surgery represents the first choice of treatment. Optimal approach varies in relation to the characteristics of the neoplasms and patients, and to surgeon's experience. The main surgical approaches are: transcervical or transcervical-transparotid route with mandibulotomy in selected case as recurrency, malignancy or huge size of the lesion; mininvasive transcervical endoscopic route; transoral endoscopy or robotic surgery; transnasal access to the upper part of the PPS; microdebrider assisted cavitation or intracapsular enucleation reserved for schwannomas; in some cases, a combination of different techniques may be used (3).

Due to all those characteristics of PPS and its tumors, surgical treatment and histological diagnosis could be challenging even for expert surgeons and pathologists.

CASE REPORT

Pre -operative assessment

We present a case of a 48-year-old man who came to the emergency room with a 2-months history of dysphonia and dysphagia. On physical examination it was evident a large neck mass of the left parotid region extended along the lateral cervical region and a prominent medialisation of the same-side lateral wall of the oropharynx. Videoendoscopy revealed a submucosal mass occupying the nasopharynx, descending along the left lateral wall of the pharynx and reaching the pharyngeal-epiglottic fold. A TC scan and an MRI (Fig.1) were performed. MRI showed a voluminous solid expansive neoplasm (7x4x7.5 cm) in the left parapharyngeal/masticatory spaces reaching cranially the nasopharynx, without a clear plane of cleavage towards the left medial ptergoid muscle and inferiorly touching the left submandibular salivary gland, without a clear plane of cleavage. The findings suggested a parotid origin of the lesion; the tumor presented heterogeneous enhancement after contrast injection. There were no gross lymphadenopathies identified in the laterocervical area. A fine-needle aspiration was executed, but the cytological examination was inconclusive, without evidence of any malignant cells. Considering dimensions and extension of the mass the surgeon's initial early decision was to proceed with a transcervical-transparotid route.

Surgical procedure

Nerve Integrity Monitor (NIM) for facial nerve was used. A Blair modified incision was performed and the skin flap elevated. The following structures were identified and preserved: the anterior margin of the sternocleidomastoid muscle and the posterior belly of the digastric muscle, the internal jugular vein, the spinal accessory nerve, the hypoglossal nerve and the external carotid artery.

After identification of the cartilaginous pointer, the common trunk of the VII cranial nerve was identified; its main branches have been followed and spared (Fig. 2A). The superficial lobe of parotid gland has been also spared. After excision of the deep lobe of the parotid gland, the PPS has been reached and the giant mass exposed. Thus, it has been gently freed and removed by finger dissection (Fig. 2B). At this point the neoplasm seemed to have been completely

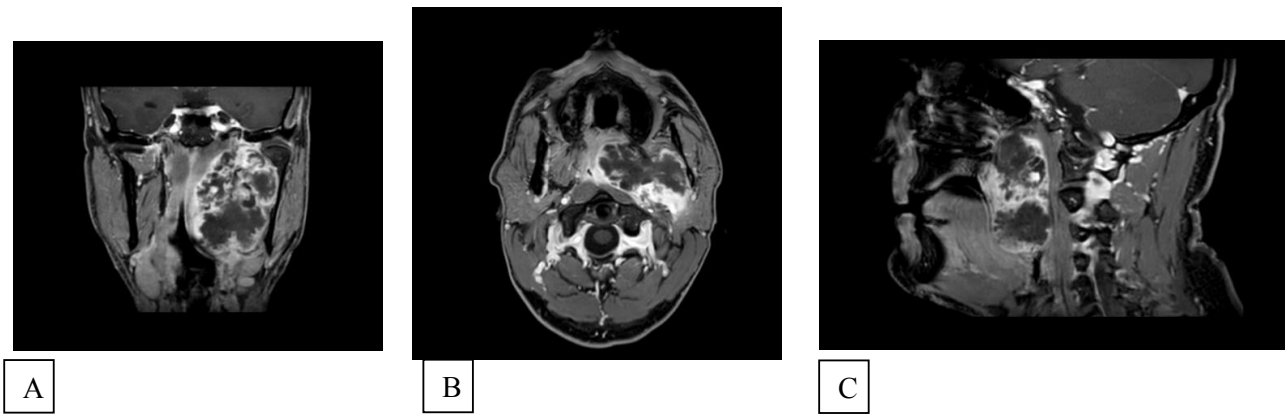

Fig. 1. *MRI. A) coronal plane; B) axial plane; C) sagittal plane.*

removed. An endoscopic check of the surgical field was performed: a small residual of tumor was seen at the most cranial and medial part of the PPS. (Fig. 2C) So, it was completely removed under endoscopic view (Fig. 3).

Post-operative evaluation

The postoperative period was uneventful. No cranial nerves palsy occurred. Three days after surgery the cervical drainage was removed and 5 days after surgery the patient was discharged. No signs of recurrence were noted at follow-up MRI after 6 months.

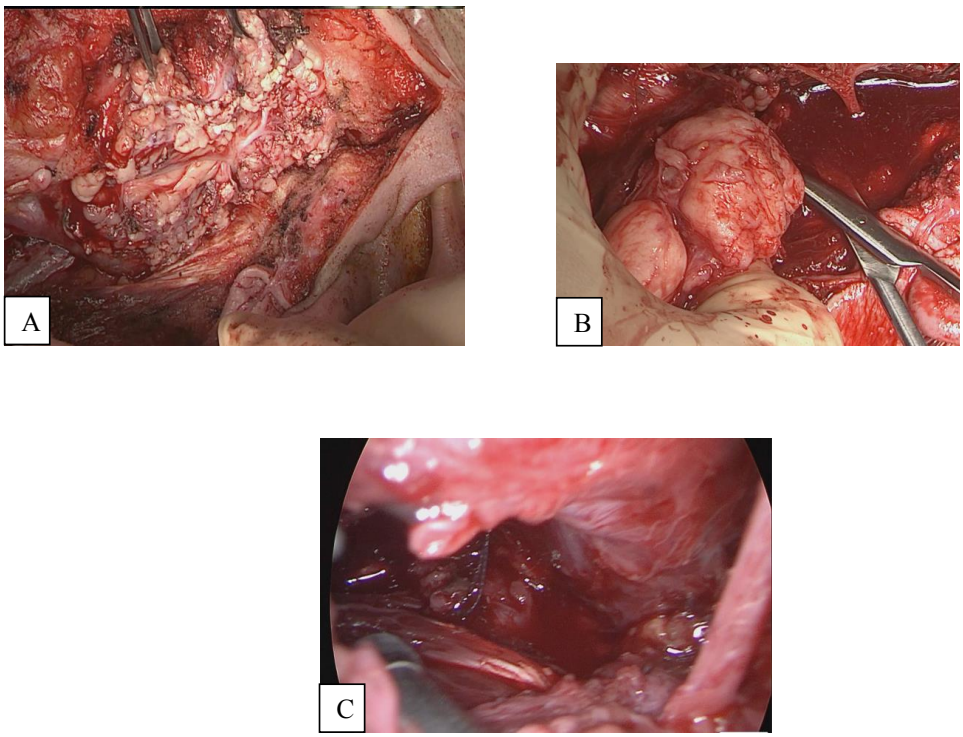

Fig. 2. *Surgical steps.* ***A)*** *identification of facial nerve;* ***B)*** *tumor dissection;* ***C)*** *endoscopic view of residual of tumor.*

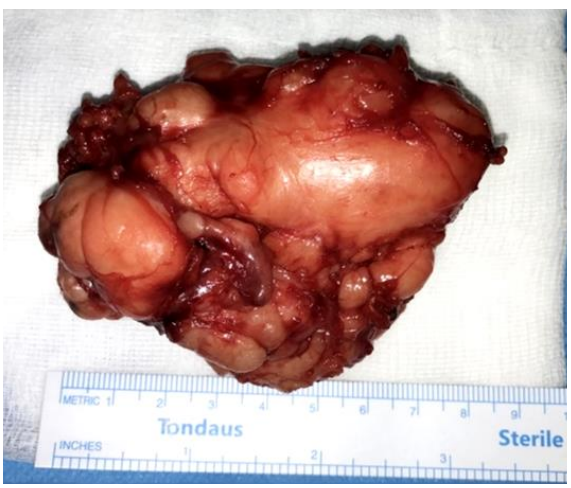

Fig. 3. *Surgical specimen.*

DISCUSSION

The complex anatomy of the PPS makes the management of tumors of this area a challenge when it comes to choosing the most suitable surgical approach. Anatomically, the PPS is a crucial area since it contains important structures as: cranial nerves IX, X, XI and XII, the internal giugular vein (IGV), the carotid artery with its bifurcation, the internal maxillary artery, the ascending pharyngeal artery and the venous plexus. This tricky space can be anatomically divided by the styloid fascia into anterolateral (pre-styloid) compartment, and a posteromedial (post-styloid) compartment. So, approaching the PPS, the surgery must not only aim at removing the tumor but to do so without compromising the nervous function (2, 4).

The surgical approach to giant lesions could be demanding when the neoplasm reaches the masticatory space, skull base or overcome the median line through the prevertebral space. Different surgical approaches have been described. In each case the choice of the best surgical strategy should be guided by the size, the position, the radiological aspects of the lesion, and the cytological/histological results.

The most common surgical technique to the PPS is the transcervical approach that provides a wide exposure of the superficial area of the PPS. In case of a benign tumor arising from the deep parotid gland lobe, the superficial lobe can be spared. This guarantees a better aesthetic result for the patient and provides an anatomical covering that protects the facial nerve, this is known as the transcervical-transparotid approach.

In selected cases mandibulotomy can be required in addition to a transcervical approach when a wider view of the PPS is required. These cases include malignancy, recurrency, lesions with a high vascular pattern or involvement of major neck vessels.

Recently some authors have proposed a minimally invasive transcervical approach using the endoscope through a small incision performed below the mandibular angle, at the level of the digastric muscle. According to Pilolli et al. (5), risk. However, is safe and allows a better visualization of the surgical plane of cleavage and a reduction of the bleeding risk, however it is not suitable for giant masses (larger than 7 cm in its widest dimension) and not recommended in malignant neoplasms (6).

Exclusive transoral approaches have caused even more debate. This technique is limited by a narrow access to the PPS and consequently causes a more challenging identification of neurovascular structures and a higher risk of surgical complications. The introduction of the new technologies as endoscopy and transoral robotic surgery (TORS) have improved the use of this technique by amplifying the surgeon's field of vision and as such reducing the percentage of intraoperative and postoperative complications. However, this approach is not suitable if the lesion extends laterally or encases a major vascular structure (3). The TORS usually implies an intraoperative fragmentation of the tumors, in particular for prestyloid lesions in more cases than the transcervical procedures (7, 8).

More recently a transnasal endoscopic access has been described. This approach passes through the infratemporal fossa and uses the Eustachian tube as an essential landmark. Excisions of lesion en-bloc have been described. Nevertheless, the indications for an exclusive transnasal procedure are very limited (9).

In alternative, transoral and transnasal approaches can be combined with a transcervical approach when the mass invades masticatory muscle space, the pterygopalatine fossa, or reaches the postero-lateral wall of the pharynx, and the upper part of PPS (10). In our case the excision of the neoplasm was performed with a transcervical transparotid approach combined with the use of endoscopy via the transcervical surgical skin incision.

Considering the characteristics of the mass the exclusive transoral or transnasal approach would not be feasible as this approach provides best the exposure only of the superomedial PPS (11). In addition, a combined transoral/transcervical could be an option when approaching this mass but would clearly convey an increased risk of an oral fistula and spreading of neck infection. On the other hand, a minimally invasive transcervical surgery would not be appropriate primarily due to the mass size but also given the extension to the masticatory space and nasopharynx without a clear plane of cleavage to the medial pterygoid muscle.

The transcervical-transparotid approach was chosen owing to the need for a wider exposure of the PPS and considering the absence of pathological tissue in the superficial lobe of the parotid gland, showed by the MRI and TC exams. Yet the exclusive transcervical technique seemed to be insufficient to guarantee a complete mass excision since the surgeon is

'blind' to the deeper and upper area of the PPS. To overcome this limitation, after a near total removal of the neoplasm, we used a 0° optic endoscope to examine this region. As described above, with this technique we were able to uncover a residual macroscopic portion of the tumor located in the upper part of the PPS and thus perform a complete excision of the tumor that appeared adherent to the nasopharynx postero-lateral wall. Another aspect of this case was the challenging histopathological diagnosis.

Over 70 different types of tumors have been described arising from the structures content in the PPS, and most of them are rare neoplasms. The most frequent source is the parotid gland (pleomorphic adenomas, adenoidocistic carcinomas), but also nerves (e.g., neuromas, paragangliomas or neurofibromas), vessels (e.g., hemangioma or aneurysms) and other tissues (e.g., meningiomas, condrosarcomas, rhabdomyosarcomas) could be the origin of the tumors.

Due to the variety of histological types also the histological analysis could be challenging as in the case reported. Indeed, the first histological response from our hospital's anatomopathological unit deposed for Teratoma with immature heterologous component; due to the rarity of this diagnosis a second opinion was requested to the Brescia hospital's anatomopathological unit and the definitive diagnosis of Pleomorphic Adenoma with extensive squamous metaplasia was defined without evidence of squamous cell carcinoma.

CONCLUSIONS

The endoscope should be considered a crucial part of the surgical armamentarium in the approach of PPS masses. The endoscope in transcervical approach to PPS allows not only a magnification of the anatomical structures but also assists the surgeon on thoroughly examining the PPS in all its extension. Furthermore, the endoscope avoided the combination of techniques that might create a communication between the cervical soft tissue and the aereo-digestive tract, reducing associated comorbidities.

Declarations:
*Conflict of interes*t: The authors have no financial relationship to disclose.
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Ethical approval: All procedures performed in studies involving human participants conformed to the ethical standards of the Institutional and/or National Research Commission and the 1964 Declaration of Helsinki and its subsequent amendments or comparable ethical standards. The Clinical Trials Ethics Committee of the Provinces of Verona and Rovigo exempted this study from its approval. All authors read and approved the manuscript.

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Case Report

ORBITAL METASTASES FROM UNDIAGNOSED BREAST CANCER: CASE REPORT AND NARRATIVE REVIEW

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ABSTRACT

Orbital metastases (OMs) are rare evidence and breast cancer (BC) is accountable for almost 40% of the cases. Nevertheless, 19% to 25% of patients may not have history of primary tumor when presenting with ophthalmic symptoms that may denote the first clinical complaints. The authors report a case of a 72 years-old woman with OM from undiagnosed BC presenting with enophtalmic syndrome, treated with chemotherapy and letrozole and alive at 3-years follow-up. A narrative review of the literature was carried out considering case reports and case series with no limitations of time. Outcomes were identified as presence of clinical/radiological orbital metastases from breast cancer with histopathological identification and presence of treatment protocol for the patients. The review included 31 patients with average age of 60 years old. Primary BC was undiagnosed in 35% of the cases and presented with ophthalmic syndrome. Estrogen receptors were expressed by 77% of the tumors and located mainly in orbital fat pad and extraocular muscles causing diplopia and movement limitations. Enophtalmic syndrome (19%) was rarer than proptosis (32%). Therapeutic strategies included radiotherapy, chemotherapy and anti-hormonal therapy. 12 months follow-up has been reported for 50% of the patients and 73% were alive. OMs from breast cancer may represent the first manifestation of BC. Clinical presentation is usually subtle and gradual and its recognition it's of primary importance. Nonetheless, since OMs represent an advanced disseminated disease, prognosis remains poor. The reported case highlighted that orbital metastases must be suspected in non-traumatic enophtalmic syndrome.

KEYWORDS: *orbital metastases, cancer*

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INTRODUCTION

Orbital metastasis is rare evidence that may occur in 2 to 3% of the patients with cancer (1). According to the current literature, breast cancer accounts for almost the 40% of orbital metastasis (2). Although this condition is rare, 19% to 25% of patients may not have history of systemic cancer when presenting with ophthalmic symptoms and thus, orbitary or ocular abnormalities may represent the first clinical complaint (1). The authors report a case of orbital metastasis from undiagnosed breast cancer presenting with enophthalmic syndrome.

CASE PRESENTATION

A 72-year-old female complained of headache with left eye enophthalmos 3 months before referral to us. Magnetic Resonance Imaging (MRI) showed inflammatory involution of the retrobulbar fat tissue of the left orbit and the patient was initially diagnosed with retrobulbar cellulitis. Antibiotic treatment (linezolid + moxifloxacin) for 15 days did not improve clinical complaints (Fig. 1).

On the first examination at our department, the patient presented left enophthalmos and recently onset diplopia on superior and right gaze. Visual acuity was preserved, and no palpable mass were detected on clinical examination (Fig. 2).

An incisional biopsy of the peri-orbital altered fat tissue of the left orbit was performed under general anesthesia. Histopathological examination reported the presence of orbital metastasis from infiltrative lobular breast cancer, ER+ (estrogen receptor) and HER2+.

Total body CT scan showed complete fat tissue replacement of the left orbit with hypervascularization, a 2 cm nodule in the right breast (BIRADS 6) and multiple bone metastasis (sternum, ribs, backbone, pelvis and femurs). An ultrasonography-guided fine needle aspiration of the breast nodule and axillary lymph-nodes was performed, and it confirmed the diagnosis of lobular infiltrating carcinoma with axillary node involvement (Fig. 3).

Chemotherapy with Paclitaxel + Pertuzumab + Trastuzumab scheme for three months was the treatment of choice. Strict follow-up was started, and CT scan after 3 months show no disease progression accompanied by clinical improvement of diplopia and headaches (Fig. 4).

After three years of therapy (pertuzumab + trastuzumab + letrozole) the disease is still under control with no clinical or radiological evidence of progression. A slight deficit in left eye elevation due to inferior rectus and inferior oblique involvement is still observable and diplopia remained stable in the extreme superior and right position of the gaze. Visual acuity is still intact and performance status of the patient is 0 (ECOG scale).

MATERIALS AND METHODS

This review was carried out with a narrative approach that highlights

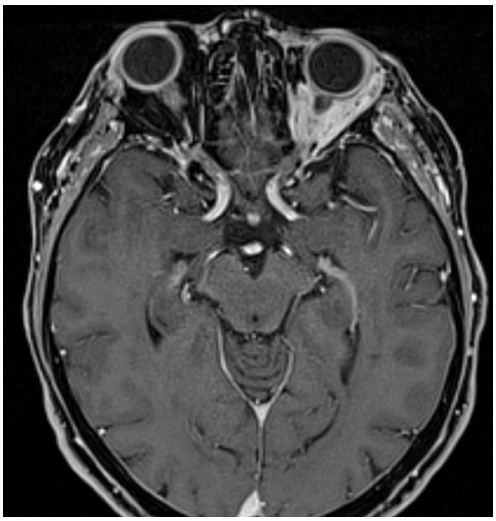

Fig. 1. *Inflammatory involution of the retrobulbar fat tissue of the left orbit.*

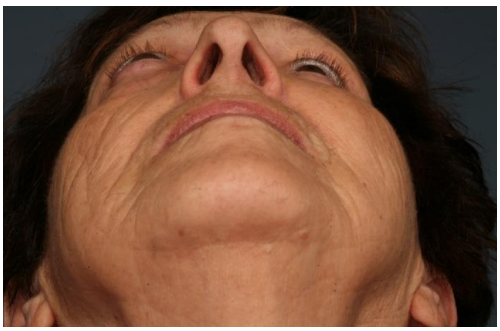

Fig. 2. *Left enophthalmos.*

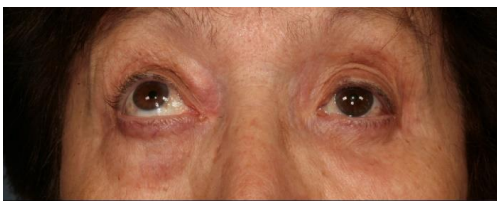

Fig. 3. *Fat tissue replacement of the left orbit with hypervascularization*

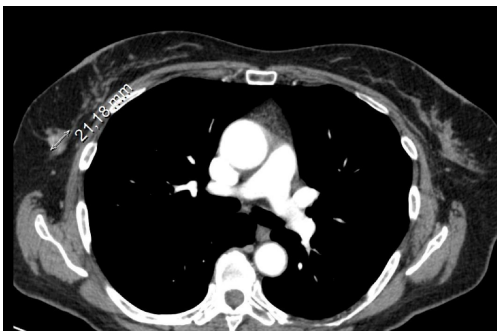

Fig. 4. *Total body CT scan.*

main findings of literature about the specific topic to outline and to improve knowledge in this field. Specifically, concepts proposed by Egger et.al were pursued to perform a narrative review of the literature according to the following steps (Table I).

Step I: formation of a four-member working group. Each of them performed as methodological reviewer and all of them also as clinical experts.

Step II: Formulation of review questions derived from up-to-date findings on orbital metastasis from breast cancer, clinical features and treatment choices. This represents a pivotal step to effectively build a search strategy.

Step III: using keywords "orbital metastasis" and "breast cancer" to perform search in databases (PubMed, PMC). Boolean operators as well as the Mesh terms were not applied to minimize potential restrictions in finding results. Inclusion article criteria were original articles, related only to humans, without limitation of publication date, no limitation about the study design were applied. Exclusion article criteria were articles for which full text was not available, were not in English, or were grey literature. Reviews and meta-analyses were excluded. Duplicate articles were eliminated and, from the articles retrieved in the first round of search, additional references were identified by a manual search among the cited references. Process of literature selection was reported following the PRISMA statement guidelines. In order to clarify the topics of this review, outcomes were identified as follows: presence of orbital metastasis from cancer (clinical and/or radiological signs and symptoms) with histopathological identification of primary tumor and presence of protocol for the treatment of the patients.

Step IV: analysis of all data extrapolated was carried out by authors and Table II was designed to present data in form of narrative review in the results section of this paper.

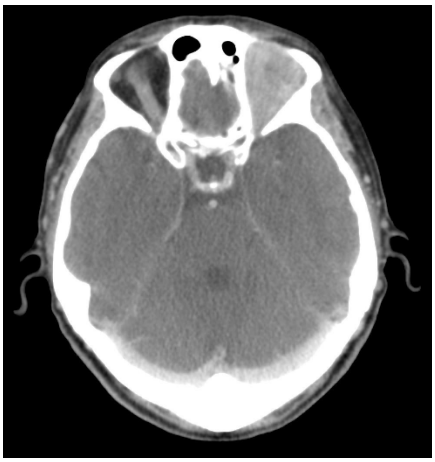

Fig. 5. *Scan at 3 months.*

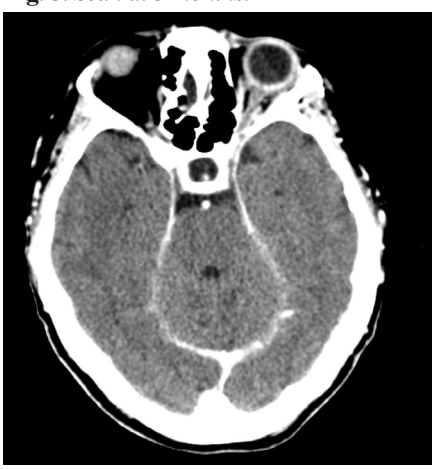

Fig. 6. *After three years of therapy (pertuzumab + trastuzumab + letrozole) the disease is still under control with no clinical or radiological evidence of progression.*

RESULTS

The considered articles were all case reports of orbital metastasis from breast cancer. Studies' year of publication ranged from 1991 to 2022.

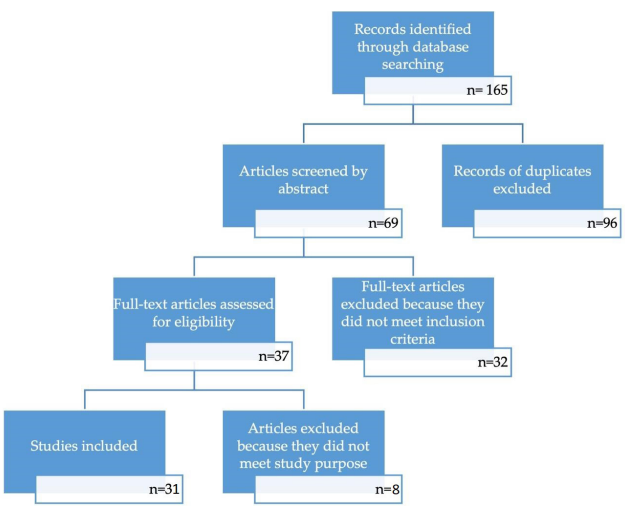

Fig. 7. *Article selection process.*

The papers included 31 patients overall, 100% of which were female. Ages ranged from 32 to 84 years with an average of 60 years. Primary breast cancer (BC) was diagnosed after the orbital finding in 35% of the cases, while 55% of the patients had previous history of BC. In two cases primary breast tumor remained occult and it was diagnosed only because of the orbital metastasis. The most common histology was the ductal infiltrative breast cancer (48%), followed by the lobular breast cancer (45%). Estrogen receptors were expressed by the 77% of the patients while 61% were positive to progesterone receptors. Moreover, HER2/neu was found positive in 17 patients, but in 12 articles the authors didn't express whether it was expressed or not.

The left to right orbit involvement ratio was 1.3 and 5 patients presented bilateral metastasis. Clinical presentation was heterogeneous but most of the patients presented movement limitations (58.06%) and diplopia (38.71%) due to extraocular muscles involvement (48% of the cases). 32% showed proptosis as presenting sign, while enophthalmic syndrome was rarer (19%).

Finally, survival at 12-month follow-up from orbital metastasis diagnosis was carried on for 15 patients and 73% were reported to be alive. Results are reported in Table II.

Table I. *Methodological approach to review.*

Step	General Activities	Specific Activities
I	Formation of working group	Four maxillo-facial and one ENT surgeon expert in head and neck anatomy and orbital surgery, as clinical and methodological operators
II	Formulation of the review questions	Evaluation of case reports of orbital metastasis from primary breast cancer. Analysis of main clinical features, demography and treatment choices.
III	Identification of relevant studies on PubMed and PMC	1. Identification of keywords in the field of interest
		2. Use of Boolean operator (AND)
		3. Inclusion criteria: no time limitation for works published; language: English; all types of full text articles. Exclusion criteria: no full text available, reviews of the literature and reviews of the literature with meta-analyses
		4. Elimination of duplicates
		5. Manual search through the references in selected articles
IV	Analysis and presentation	Extrapolation of data from all revised studies and their presentation in form of narrative review

Table II. *Articles included in the narrative review and summary of the results.*

Authors	Title	Sex	Age	Orbit (L, R, B)	Ocular symptoms	Orbital region	Other metastasis	PT diagnosis	Primary Lesion (histop)	Breast (L, R, B)	ER	PR	HER2	Treatment	Treatment result	Survival
Alameddine et al.(16)	**Orbital fat regeneration following hormonal treatment of metastatic breast carcinoma**	F	76	R	Enophtalmos, movement limitation	Fat tissue	Bone marrow	Later	ILBC	B	1	1	1	Letrozole;		>120m
Coutinho et al.(17)	**Extraocular Muscles Involvement as the Initial Presentation in Metastatic Breast Cancer**	F	68	L	Diplopia, ptosis, retrobulbar tenderness	Fat tissue		Later	IDBC	R	1	1	0	Docetaxel; epirubicine; anastrozole		38m
Diltoer et al.(18)	**Breast Cancer Metastasis Presenting as Conjunctival Chemosis**	F	72	R	Pain, chemosis, palpable mass	Conjunctiva, lacrimal gland	/	Before (25y)	ILBC	R	1	/	/	**ND**		/
El Bakraoui K et al.(19)	**Orbital Metastasis from Triple-Negative Breast Cancer: Case Report and Literature Review**	F	43	L	Palpable mass; slight reduction visual acuity	Orbital bone roof;	Pulmonary, liver	Before (3m)	IDBC	L	0	0	0	QT neo, radioterapy, QT adiuvante		12m
El-Khatem Dupuis et al.(20)	**Enophthalmos as the Initial Systemic Finding of Undiagnosed Metastatic Breast Carcinoma**	F	74	L	Enophtalmos, ptosis, diplopia, movement limitations	Fat tissue	Bone marrow	Undiagnosed	ILBC	L	1	1	0	Letrozole, Palbociclib	OM stability	>72m
		F	72	R	Enophtalmos, ptosis, retrobulbar tenderness, movemente limitations	Frontal bone, lacrimal gland, EOM, ON,	Bone marrow, mediastinum, lymphnodes	After	ILBC	L	1	1	0	Letrozole, Palbociclib + RT + CS (OM)	Progression	36m
Framarino-Dei-Malatesta M et al.(21)	**Metastases to extraocular muscles from breast cancer: case report and up-to-date review of the literature**	F	44	R	Diplopia, blurred vision, movement limitation, vision acuity decreasement	Inferior rectus	/	Before (7y)	ILBC	R	1	1	0	RT + fulvestrant (OM) + palbociclib	Mass regression, no vision improvement	>20m
Glazer et al.(22)	**Orbital metastasis as the presenting sign of adenocarcinoma of the breast**	F	64	R	Eyelids swelling, proptosi, chemosis	Fat tissue, EOM	Yes	After	Adenocarcinoma	L	/	/	/	RT	Progression	12m
Gupta et al.(23)	**Unilateral orbital pain and eyelid swelling in a 46-year-old woman: orbital metastasis of occult invasive lobular carcinoma of breast masquerading orbital pseudotumour**	F	46	L	Pain	EOM	/	After (3m)	ILBC	B	1	1	0	Surgery + tamoxifen + leuprolide.	Regression	>6m
Karti et al.(24,25)	**Orbital Metastasis Secondary to Breast Cancer: A Rare Cause of Unilateral External Ophthalmoplegia**	F	78	L	Diplopia, movement limitations, ptosis	EOM (medial rectus), III cranial nerve	Bone, adrenal	Before (1y)	ILBC	R	1	0	/	QT + RT (OM)	/	/
Lin et al.(25)	**Adjuvant Intravitreal Bevacizumab Injection for Choroidal and Orbital Metastases of Refractory Invasive Ductal Carcinoma of the Breast**	F	48	B	Blurred Vision	Intraocular, orbital, optic nerve	bone, liver, lung	before (3y)	IDBC	L	1	1	1	Letrozole, fulvestrant, ribociclib, bevacizumab(intravitreal)	Regression	>6m
Milman et al.(26)	**Breast carcinoma metastatic to the orbit: an unusually late presentation**	F	83	B	Hyperglobus, movement limitation, palpable mass inferior	EOM (inferior oblique, inferior recuts, superior rectus, medial rectus)	Bone, pancreas, skeletal muscles, lymphnodes	Before (28y)	IDBC	L	1	/	/	Letrozole	Improvement ocular motility	
Mohadjer et al.(27)	**Orbital metastasis as the initial finding of breast carcinoma: a ten-year survival**	F	50	R	Pain, enophthalmos	Fat tissue (Superomedial)	Bone marrow, bone	After (2y)	IDBC	R	1	1	0	radiotherapy, chemotherapy, tamoxifen	Resolved	ND
Muhammad-Ikmal et al.(28)	**Sino-orbital metastasis as the initial presentation of advanced breast cancer**	F	70	B	Blurred vision, progressive narrowing, loss of smell, frontal headache, enophthalmos	Ethmoidal sinuses extending to the frontal sinuses and both orbits, EOM (medial rectus and superior rectus), optic nerve, preseptal region	Bone frontal, parietal, occipital, greater wing of sphenoid, mandible, pterygoid bones	After	IDBC	L	1	1	0	Chemotherapy, radiotherapy	No progression	> 12m
					limitation		region									
Nifosi et al.(30)	**Unilateral localized extraocular muscle metastasis by lobular breast carcinoma**	F	46	L	Diplopia, eye swelling, mild proptosis and movement limitation	EOM (upper oblique muscle)	Bone	Before (3y)	ILBC	R	1	1	0	Chemotherapy, stereotactic radiation therapy,	diplopia and pain disappeared	> 6 m
Oprean CM et al.(31)	**Unilateral Orbital Metastasis as the Unique Symptom in the Onset of Breast Cancer in a Postmenopausal Woman: Case Report and Review of the Literature**	F	57	L	Diplopia, reduced visual acuity, orbital tenderness, exophthalmia, ptosis, hypoesthesia of the left hemi-face, movement limitations	Fat tissue (retroocular space in the intraconal area), EOM	NO	After	ILBC	L	1	0	0	Sectorial mastectomy with ipsilateral lymphadenectomy and radiotherapy, also radiotherapy left eye, hormonal therapy POI chemotherapy	unilateral blindess secondary to irradiation. After 4 y retroocular relapse, bone metastases and periotneal carcinomatosis	48m
Papathanassiou et al.(32)	**Orbital metastasis secondary to breast cancer mimicking thyroid-associated ophthalmopathy**	F	70	L	Horizontal diplopia, movement limitation	EOM (lateral rectus muscle)	Multiple sites of metastases in bones	Before (8y)	ND	L	ND	ND	ND	Refused chemotherapy and radiation therapy	ND	ND
Park et al.(33)	**Metastatic breast cancer presenting as a subconjunctival mass**	F	41	L	Conjuntival injection and foreign body sensation	Conjunctiva	Bone marrow, muscular and subcutaneous, lung, subcranial, mesenteric, pancreatic	Before (2y)	IDBC	ND	0	0	ND	**ND**	ND	ND
Patel et al.(34)	**Gaze-evoked amaurosis from orbital breast carcinoma metastasis**	F	47	R	Transient vision loss	Fat tissue	Humeral head	Before (18m)	IDBC	B	1	1	0	**ND**		
Pinto Provença et al.(4)	**Orbital metastasis from an occult breast carcinoma (T0, N1, M1)**	F	66	L	Oedematous lower eyelid, proptosis, movement limitations	Subcutaneous tissue of the inferior eyelid	Femur, iliac, sacrum, cervical and lumbar spines, liver, gastric antral	Undiagnosed	Occult	Occult	1	1	0	Chemotherapy and hormonal therapy	Controlled	>60m
Razem et al.(35)	**An early orbital metastasis from breast cancer: A case report**	F	33	R	Diplopia, movement limitations, exophthalmos, pupillary asymmetry, hypoaesthesia	EOM (medial rectus muscle)	ND	Before (1m)	ND	L	ND	ND	ND	hormone therapy	Steady state	> 12m
Rossi et al.(36)	**An unusual orbital metastasis of breast cancer**	F	84	R	Diplopia, exophthalmos, proptosis, reduced visual acuity, pain	EOM (lateral rectus muscle)	Pleura, spleen, lung, aracardiac area and the lowertract of the retro-aortic area, lymph nodes in the mediastinum and bilateral hilar and para-aortic	Before (14 y)	IDBC	R	1	1	0	Chemotherapy with capecitabine, letrozole	Reduced tumor mass, disappearance of the symptoms	ND
Saffra et al.(37)	**Orbital metastasis as the initial presentation in bilateral lobular invasive carcinoma of the breast**	F	46	L	Dipolpia, pain exacorbated by eye movement, ptosis, chemosis, reduced visual acuity	EOM (Medial rectus muscle), mass sorrounding the distal optic nerve sheath	ND	After	ILBC	B	1	1	0	tamoxifen, leuprolide	Resolution of ocular symptoms	ND
Salinas-Botrán et al.(38)	**Orbital Metastasis in Breast Cancer**	F	60	L	Proptosis, movement limitations	EOM (inferior rectus muscle)	ND	ND	IDBC	R	1	1	0	Palbociclib e radioterapia	Resolution of the blurry vision and proptosis. Mass regression	> 6 m
Sharaf et al.(39)	**A Complete Response of Orbital Metastases in Breast Cancer Patient Treated with Oral Chemotherapy: Case Report and Literature Review**	F	46	R	Ptosis, proptosis, eye redness, movement limitation, pain in movement	EOM (superior rectus and levator palpebrae superioris muscle complex, lateral rectus muscle)	NO	Before (4y)	IDBC	L	0 poi 1	0 poi 1	0	capecitabine e vinorelbine, terapia ormonale	Ptosis reduction	> 28 m
Solari et al.(40)	**Orbital metastasis from breast carcinoma presenting as neurotrophic keratitis**	F	81	L	Redness, proptosis, exophtalmos	Left superior orbital rim extending to the soft tissues (temporally and posteriorly along the globe and lateral orbital wall), intracranial invasion	ND	Before (2y)	IDBC	ND	1	ND	ND	radioterapia		ND
Surace et al.(41)	**Orbital metastasis as the first sign of "Dormant" breast cancer dissemination 25 years after mastectomy**	F	73	L	Ptosis, diplopia, severe movement limitations, inability to close the eyelids during the occlusion, enophthalmos.	EOM	ND	Before (26 y)	ILBC	L	1	1	ND	Terapia ormonale	Mild improvement	ND
Tiwari et al.(42)	**Paranasal sinus and retro-orbital metastasis in a case of breast carcinoma: a clinicoradiological review**	F	62	L	Proptosis, visual loss, pain, subcutaneous oedema	Fat tissue (retro-orbitosphenoidotemporal region) with intracranial extension	ND	ND	IDBC	L	ND	ND	ND	Palliative RT	Symptoms regression	ND
Tsutsui et al.(43)	**Orbital metastasis of invasive lobular carcinoma of the breast**	F	58	B	Visual disturbance, bilateral peri-orbital swelling, movement limitations	Fat tissue (medial to retrobulbar)	Ribs (5 yr later), bone marrow	Before (9y)	ILBC	R	1	1	0	**NO**	Deceased	3m
Vlachostergios et al.(44)	**Orbital metastasis of breast carcinoma**	F	46	L	Diplopia, exophthalmos, proptosis, decreased visual acuity, pain	Fat tissue (inferior quadrant intra orbital)	Femur, backspine	Before (4y)	IDBC	L	1	1	0	Docetxel e capecitabine, poi cyberknife image-guided stereotactic radiosurgery system in one session	Symptoms regression, volumetric reduction	> 18m

DISCUSSION

Orbital metastasis accounts for 1-13% of all orbital neoplasms and affects 2-5% of patients with distant malignancies (2-6). Among primary solid tumours, breast cancer is the most frequent source, and it is responsible for around 39% of the orbital metastasis (2).

Age is an important risk factor and patients in their 6th decade or older are the most affected. Usually, a previous diagnosis of solid tumour is reported, but in around 19% of the cases, as well as in the case presented, orbital manifestations represent the first sign of breast cancer (6). Thus, accurate identification of orbital signs is of primary importance in undiagnosed patients.

Orbital metastases are commonly unilateral rather than bilateral(3). The latter is commonly seen in breast cancer (20%) compared to other primary tumours (4%). According to the literature, metastasis from breast cancer often infiltrates extraocular muscles and the surrounding orbital fat tissue (7, 8). In the present review, 38% of the OMs infiltrated orbital fat tissue and 48% affected EOMs. Other metastasis sites were the orbital bone, eyelids, lacrimal gland, optic nerve and cranial fossa.

Clinical displaying of orbital metastasis can be variable. Based on a case series by Ahmad et al. (9), diplopia (48%), exophthalmos (26%), pain (19%), decreased vision (16%), ptosis (10%), and palpable orbital mass were most common symptoms (10). Even though enophthalmos is decidedly rarer than exophthalmos (3), the recognition of this unique syndrome is of great diagnostic importance because it seems to have a more insidious onset and gradually progressive course (10, 11). The hypothesis is that tumour-induced desmoplasia, fibrosis, muscle invasion and/ or fat atrophy can be responsible for the ocular globe inward traction (12). As in the reported case, in some patients, enophthalmos could represent the first and only presenting sign of breast cancer metastasis and thus its recognition could lead to an earlier diagnosis of the primary tumour. Therefore, a gradual onset of non-traumatic enophthalmic syndrome must alarm of metastatic orbital disease.

Magnetic Resonance Imaging is an important diagnostic tool in orbital masses but biopsy with histopathological examination represents the gold standard. Infiltrative lobular breast cancer (ILBC) is the most relevant histology encountered as an OM source while ductal breast cancer (IDBC) has a higher prevalence in primary breast cancer (13). While the present work found an IDBC to ILBD ratio of 1,07, almost 80% of the biopsy specimens were positive to estrogen receptors. The orbital fat pad may attract the dissemination of breast cancer cells with local production of steroid hormones used to regulate tear film composition(14, 15). Still, the exact mechanism needs further investigation. Alternatively, OMs from ILBC may simply extend to the orbit from nearby bone or meningeal metastases.

The presence of OM represents an hematogenous disseminated advanced breast cancer disease. Thus, the prognosis after OMs diagnosis is usually poor and it is reported to be around 15.6 months after the diagnosis. Only 16 studies reported follow-up data. 12 of the 17 patients were alive at the 12 months follow-up, while 5 patients died in the first year after the diagnosis. In contrast to the average survival reported in literature, our patient is still alive at 3-years follow-up. Therapy of OMs is usually palliative, and it is aimed at improving quality of life rather than improving prognostic outcome. Due to high prevalence of estrogen receptor positivity among biopsy specimens, anti-hormonal therapy (i.e., Letrozole) is often used as in the 48% of the reported cases. Beside this, chemotherapy and radiotherapy are alternative treatment evolving strategies. Twenty-eight authors reported treatment strategies and 50% used RT, while chemotherapy has been administrated in 68% of the patients. Extensive orbital surgery is not generally recommended due to its morbidity and poor impact on patients' prognosis (8) and should be limited to unmanageable clinical symptoms.

CONCLUSIONS

Orbital metastasis from breast cancer is a rare occurrence that may represent the first manifestation of this solid tumor. Clinical presentation may be subtle and gradual and its recognition it's of primary importance to improve patient's survival. Nonetheless, since OMs represent an advanced disseminated disease, prognosis remains poor.

CONSENT STATEMENT

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

CONFLICT OF INTEREST

No conflict of interests was declared by the authors.

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