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CASE-BASED UPDATE

Gradenigo's syndrome with abscess of the petrous apex in pediatric patients: what is the best treatment?

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Abstract

Background Gradenigo's syndrome is defined by the classic clinical triad of ear discharge, trigeminal pain, and abducens nerve palsy. It has become a very rare nosological entity after the introduction of antibiotics, so that has been defined as the "forgotten syndrome." However, the underlying pathological process (apical petrositis) still represents a life-threatening condition that shall be immediately recognized in order to address the patient to the proper therapy. The therapy itself may be an argument of discussion: on a historical background ruled by surgery, reports of successful conservative antibiotic treatment have risen in recent years.

Methods and Results We reported a case of Gradenigo's syndrome in a child with an abscess of the left petrous apex and initial involvement of the carotid artery. After multidisciplinary evaluation, we decided to encourage conservative treatment, until complete regression was observed.

Discussion The available literature of the last 10 years was reviewed, with particular attention to the presence of an apical abscess and the therapeutic approach. The principles of management with regard to conservative therapy versus surgical indications are therefore examined and discussed.

Keywords Abducens · Apicitis · Surgery · Conservative · Antibiotic

Introduction

Gradenigo's syndrome (GS) is a rare disease that presents with a clinical triad of otitis media (OM) with otorrhea, pain in the region of the trigeminal nerve, and diplopia with ipsilateral abducens nerve palsy. First described by Giuseppe Gradenigo, professor of the University of Turin in 1904, GS represents a particular clinical picture secondary to an infectious process of the petrous apex (PA), a rare complication of OM [1].

The exact incidence of the disease is unknown, but as reported in the literature, intracranial and extracranial complications of OM have become rare after the introduction of antibiotics; to date, the incidence reported in the literature of intracranial complications is about 0.04-0.15% [2, 3]. While in 1937 the apical petrositis (AP) occurred in 0.3% of the cases of OM, nowadays its incidence has been estimated at 0.002% [4]. Although acute OM represents the most common etiology of AP, chronic OM with or without cholesteatoma has also been reported [5–7].

The clinical signs of GS are secondary to an infection of the PA, which is in a strict anatomic relationship with the V and VI cranial nerve course. More in detail, the sixth cranial nerve reaches the cavernous sinus through a structure called Dorello's canal. This structure is in strict proximity to the PA, and here the abducens nerve is susceptible to be involved by the pathological process. On the other hand, the deep facial pain may be related to direct irritation of the gasserian ganglion in Meckel's cave to the involvement of the overlying dura mater, which is innervated by the trigeminal nerve [6].

Hereby we present the case of a child with Gradenigo's syndrome caused by an abscess of the PA. Clinical patterns, as well as diagnostic and therapeutic features of the case, will be presented and discussed.

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Case report

R.F. was an 11-year-old boy, weighed 43 kg. He was born at term, after an uncomplicated pregnancy. From the age of 4 years, he started to suffer from recurrent upper airways infections, frequently resulting in episodes of acute OM treated with antibiotic therapy and steroids. In January 2017, he presented a new episode of left acute OM in absence of fever or other systemic symptoms so that oral antibiotic therapy (amoxicillin + clavulanic acid 1 g twice a day for 8 days) was administered by the family pediatrician with initial improvement in the clinical conditions. Two days after the conclusion of the therapy, due to recurrence of left ear pain and the detection of a persistent otoscopic picture of OM, a second antibiotic (oral cephalosporin) was administered.

At the beginning of February, the child showed no improvement of the symptom complex; moreover, due to the sudden onset of left ear discharge, headache, left retro-orbital pain, and diplopia, he was brought by the parents to the emergency department of our institution. At admission to our pediatric department, the patient presented afebrile, showing gaze palsy with the specific limitation of the abduction movement of the left eye (Fig. 1), complaining of left purulent otorrhea, deep retro-orbital oppressive pain, and pain in the region of the first and second branches of the V cranial nerve. All the vital signs and parameters were normal. Blood exams revealed CRP 4.24 mg/dl; WBC 10.640/mm^3; N 6500/mm^3). ENT counseling was immediately performed. Otomicroscopy showed normal findings of the right ear and confirmed left purulent otorrhea with perforation of the posteroinferior quadrant of the tympanic membrane. Clinical signs of acute mastoiditis were absent (absence of hyperemia and swelling of the mastoid area, absence of lateralization of the pinna, normality of the posterosuperior aspect of the external auditory canal). The audiometric evaluation showed left mild conductive hearing loss with pure tone average (PTA, calculated at 0.5, 1, 2 kHz) of 45 dB HL and the normal audiometric threshold of the right ear. Speech audiometry confirmed left conductive hearing loss. An auricolar swab was performed but returned negative in the subsequent days. Clinical examination of the cranial nerves function confirmed left VI cranial nerve failure with palsy of the left eye in lateral sight movement (Fig. 1). III, IV, VII, IX, X, and XI cranial nerves function was bilaterally preserved. The child underwent high-resolution computed tomography (HR-CT) of the skull base in the same day, showing opacification of the left PA consistent with substitution of the normal areation of the PA with a soft-tissue density material, with signs of initial coalescence and destructuration of the bony cellularization (Fig. 2). A brain magnetic resonance imaging (MRI) was immediately performed (Fig. 3), revealing T1 isointensity of the PA with partial substitution of the normal hyperintensity of the clival bone marrow due to inflammation. The left PA appeared hyperintense in T2-weighted scans. After contrast administration, an enhancing rim outlined the presence of an abscessual cavity within the PA [8]. Initial involvement of the horizontal tract of the internal carotid artery (ICA) in absence of signs of intravascular involvement was evidenced by contrast enhancement of the adventitia of the vessel. Diffusion-weighted imaging (DWI) confirmed the abscessual nature of the lesion of the left PA [9]. The patient was immediately hospitalized and a triple intravenous antibiotic therapy was started with ceftriaxone 1 g twice a day, metronidazole at 7.5 mg/kg every 8 h, and teicoplanin at 10 mg/kg every 12 h for the initial three doses and then at 5 mg/kg/day at steady state. Intravenous methylprednisolone was also administered in order to control pain and reduce inflammation. After orthoptics evaluation, an eyepatch was applied to the left eye, to provide relief from the discomfort deriving from diplopia.

Close clinical follow-up showed improvement of the general condition of the child over the first 72 h with a decrease of CRP and WBC, resolution of the retro-orbital pain, and improved oculomotricity; the search for urinary streptococcal antigen also came back negative. Repeated color-doppler studies of the supra-aortic vessels were performed in order to promptly detect worsening of the carotid blood flow and to monitor the jugular outflow. On the 7th day of admission, CRP returned to normal range. On day 8, an angio-MRI of the brain evidenced volumetric reduction of the abscess, improvement of the inflammatory process of the ICA, and excluded

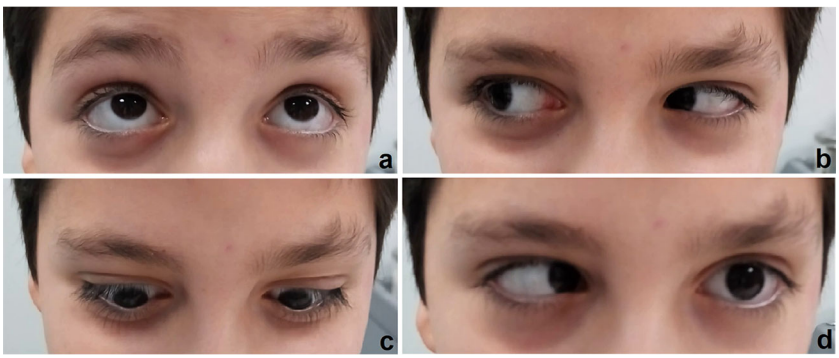

Fig. 1 Upward (**a**), rightward (**b**), downward (**c**), and leftward (**d**) gaze clinical examination showing selective impairment of the left VI cranial nerve

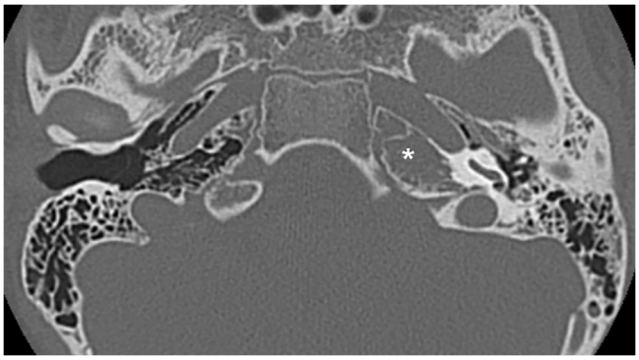

Fig. 2 CT findings consistent with left petrous apex opacification with coalescence of the bony cellularization (asterisk)

thrombotic involvement of the major intracranial sinuses. A second CT scan excluded progression of coalescence of the PA bony trabeculae.

At day 21, teicoplanin was stopped and the patient was discharged. We continued outpatient follow-up, progressively reducing the ongoing therapy until metronidazole and ceftriaxone were stopped at day 35. Methylprednisone was switched to oral prednisone at discharge and steroids were stopped after dècalage. After 1 month, otomicroscopic re-evaluation assessed complete regression of the ear discharge with complete healing of the tympanic membrane perforation. Tonal audiometry performed the same day resulted normal with type A tympanogram bilaterally. The eyepatch was removed after that orthoptic re-evaluation documented full recovery of left eye's abduction movements. Long-term follow-up was conducted by the ENT specialists and pediatric neurologist and performing brain MRIs at 3, 6, and 12 months, showing a progressive return to normality of the PA (Fig. 4). The patient recovered completely and remained symptoms-free for the 30 months follow-up.

Literature review: materials and methods

The literature of the last 10 years has been reviewed in order to provide an updated picture of the disease.

Papers were sorted on PubMed using the query "Gradenigo Syndrome" and "Gradenigo's Syndrome." A total of 119 papers were found. The results were matched in order to exclude duplicates. Articles not written in English were excluded. Review articles were excluded as well. Retrospective case series referring prior to 2010 were excluded in order to provide data updated to the last decade. Papers improperly referring to GS or to AP (in which a proper diagnosis of GS could not be ascertained), as well as reports lacking sufficient data or description of the cases, were excluded.

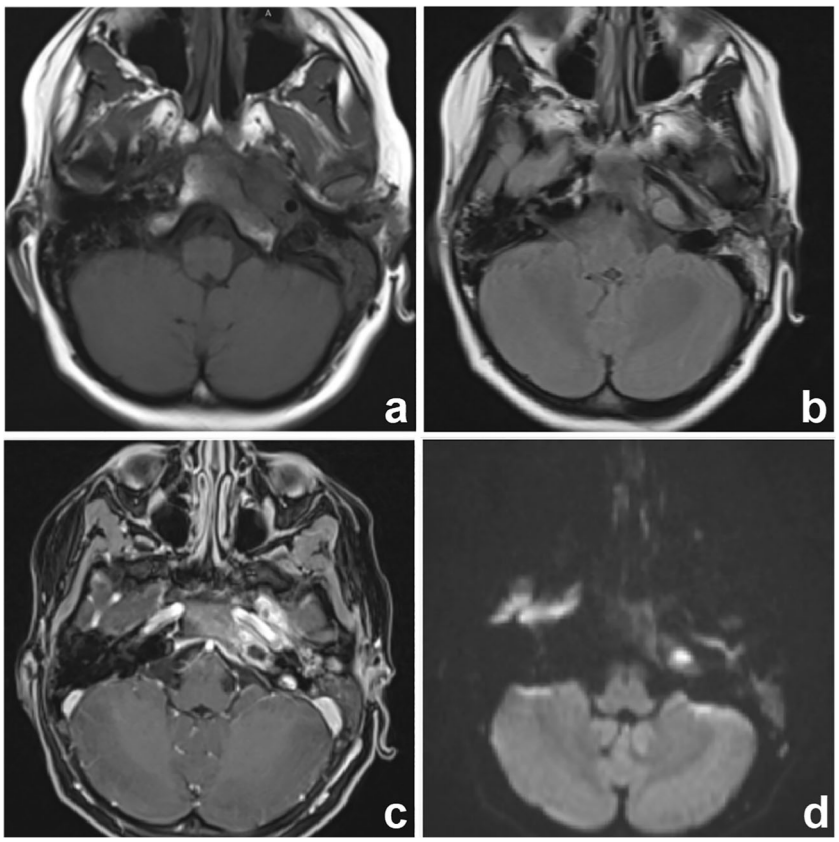

Fig. 3 MRI findings with axial T1-weighted showing isointensity of the left petrous apex (PA) with loss of the normal hyperintensity of the clival bone marrow due to inflammation (**a**), T2-weighted showing hyperintensity of left PA (**b**), and T1-weighted evidencing vivid contrast enhancement of the left PA and enhancement ring revealing an abscessual cavity (**c**). Diffusion-weighted imaging sequences showed diffusion restriction, confirming the presence of an abscess of the PA (**d**)

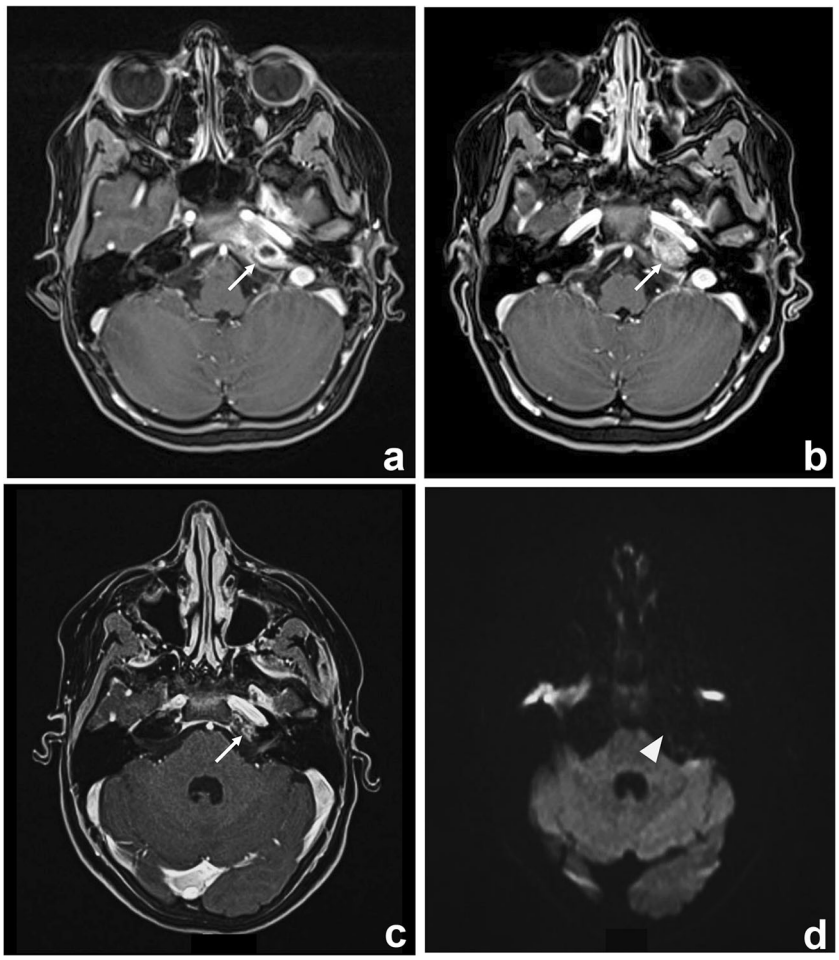

Fig. 4 Evolution of the abscessual cavity over time (white arrows). Sequential axial T1-weighted brain MRI with contrast enhancement evidencing the left petrous apex inflammation in different stages of the treatment: at the onset (**a**), at 3 months (**b**), and at 12 months (**c**). Notice the complete regression of the abscess and full pneumatisation of the left petrous apex, with diffusion-weighted imaging sequences showing no residual diffusion restriction at 12 months (white triangle). Minimal residual contrast enhancement in (**d**) is secondary to scar remodeling and healing processes of the soft and bony tissues. The patient recovered completely after antibiotic and steroid therapy, and remained symptoms-free for the 30 month follow-up

Literature review: results

A total of 21 papers were included in our review [5, 7, 9–27], for a cumulative number of 33 patients with GS reported in the last 10 years. Of these, 23 (69.7%) were patients in pediatric age, and our case brings the number to 24. Diagnosis of GS was confirmed by means of CT and MRI by all the authors. An abscessual cavity within the PA was distinguishable by the MRI pictures included in the article or from the direct statement of the author in 8 out of the 33 patients (24.2%) included in the literature. When not reported or not evident by MRI pictures, the presence of an abscess was recorded as absent. Surgical therapy was performed in 20 out of 33 patients (60.6%). Of these, 4 patients received tympanostomy tube insertion alone, 9 patients were treated with mastoidectomy and tympanostomy tube insertion, 1 with mastoidectomy alone, 1 patient received canal wall down mastoidectomy, and 1 type III tympanoplasty for coexistent cholesteatoma; 4 patients were submitted to direct drainage of the PA. Data regarding the surgical route to the PA are available for 2 out of 6 patients, in which combined infralabyrinthine/supralabyrinthine and infralabyrinthine routes were performed respectively [11]; 13 patients (39.4%) were therefore treated with conservative treatment using broad-spectrum prolonged antibiotic therapy. When considering the subpopulation of patients with abscess of the PA, surgical therapy was performed in 6 out of 8 patients (75%). More in detail, ventilation tube insertion alone was performed in 2 patients, mastoidectomy along with ventilation tube insertion in 2 patients, and direct apex drainage in 2 patients. Of these two patients, one underwent surgical apex debridement via the infralabyrinthine route [11], while specific data regarding the surgical approach are not available for the second patient[7]. Data of the patients included in the review are summarized in Table 1.

Discussion

Acute OM is a condition commonly found among young children. However, although the use of antibiotic therapy has greatly reduced their occurrence, global reports nowadays indicate a rise of complications as a result of a multifactorial process [28, 29], in which emerging antibiotic resistance seems to play an important role [30]. Nevertheless, overall we found 33 patients with GS reported worldwide in the last 10 years, and an abscess of the PA was present only in 8 of

Table 1 Review of the literature

First author	Year	Patients (children)	Abscess	Treatment
Brambilla [21]	2019	1 (1)	0	Conservative
Özkaçmaz [22]	2019	1 (1)	0	Conservative
Dorner [23]	2017	1 (1)	0	Surgery (M)
Kazemi [24]	2017	1 (0)	0	Conservative
Shapiro [25]	2017	1 (1)	1	Surgery (VT)
Taklasingh [7]	2017	1 (0)	1	Surgery (DAD)
Vitale [26]	2017	1 (1)	1	Surgery (M + VT)
Ghani [27]	2017	1 (1)	0	Conservative
Jensen [5]	2016	4 (1)	0	2 conservative; 1 surgery (TPL)
Janjua [10]	2016	1 (1)	1	Surgery (VT)
Chen [11]	2014	4 (0)	1	Surgery (3 DAD; 1 CWD)
Plodpai [12]	2014	1 (0)	0	Conservative
Heshin-Bekenstein [13]	2014	2 (2)	1	Surgery (2 M + VT)
Humayun [14]	2011	1 (1)	0	Surgery (M + VT)
Rossor [15]	2011	1 (1)	0	Conservative
Kong [16]	2011	1 (1)	0	Surgery (VT)
Ibrahim [9]	2010	1 (1)	1	Conservative
Isaacson [17]	2010	7 (7)	0	1 conservative; 6 surgery (5 M + VT; 1 VT)
Hitier [18]	2010	1 (1)	1	Conservative
Scardapane [19]	2010	1 (1)	0	Conservative
Tornabene [20]	2010	1 (0)	0	Conservative

Summary of the review conducted on the literature of the last 10 years. *VT*, ventilation tube alone; *M*, simple mastoidectomy; *TPL*, tympanoplasty (type III); *CWD*, canal wall down mastoidectomy; *DAD*, direct apex drainage surgery

them. Even assuming underestimation due to possibly unreported cases, GS remains uncommon, while the presence of an abscessual cavity in its context may be defined as anecdotal.

As previously discussed, the infectious pathology of the PA may be secondary to acute or, more rarely, chronic OM with or without cholesteatoma, as, for instance, reported by a Jensen et al. [5]. With regard to these conditions, the literature has shown the difference in the pattern of onset of VI cranial nerve palsy: it has been observed to occur from 1 week to 3 months from the diagnosis of acute OM, while its occurrence may be delayed up to 3 years in cases secondary to chronic OM [5, 7].

AP etiology has been explained through two theories: Eagleton, observing that the PA was diploic and not pneumatic in many cases, sustained that the infection may reach the PA through hematogenous spread [31]. On the other hand, Voss and Meltzer sustained the theory of the contiguous spread of the infection from an original focus located in the middle ear through the temporal bone air cell tracts [32, 33].

The clinical picture of the infections of the PA has shown great evolution through the literature of the last century: early reports considered GS as the synonym of AP, while later evidence assessed that the typical triad of GS only occurred in a little percentage of the cases [4, 6]. Moreover, a "masking" effect on the presenting symptoms has been noticed after the introduction of antibiotic therapy, thus leading to more insidious and misleading clinical pictures. In cases of AP, a middle ear infectious process is rarely absent [34]. To date, the most commonly reported clinical presentation of AP is a persistent headache or retro-orbital pain in association with ear discharge: a picture that must be considered sufficient to require further investigations by means of diagnostic imaging [4].

In those cases in which AP is suspected, imaging should comprise both HR-CT and MRI scan with contrast enhancement. HR-CT scan provides information upon bone integrity, with particular regard to the presence of lytic processes involving the PA and represents a first-line study in the purpose of a possible surgical approach. The typical finding of HR-CT scan in course of PA suppuration is increased density of the normal air cell tract that in absence of breakdown of the bony trabeculae is virtually indistinguishable from a diploic PA. Contrast enhancement MRI represents the "sine qua non" element of the diagnostic workup: typical findings are T1 isointensity of the PA and increased signal in T2-weighted scans, with vivid enhancement after Gadolinium administration, which may define an enhancing rim in case of an apical abscess [35]. Confirmation of the presence of an abscessual cavity is given by diffusion restriction at DWI [9]. Moreover, MRI may give vital information regarding the infectious

spread to the surrounding structures and the possibility of further complications.

The possible complications of a suppurative process of the PA are strictly related to the peculiar location of the infection. As a matter of fact, the suppurative process may eventually spread to the meninges or the brain (meningitis, cerebral abscess, multiple cranial nerves deficits), to the sigmoid or the cavernous sinus (phlebitis, thrombophlebitis), to the labyrinth or the internal acoustic canal (vertigo, total sensorineural hearing loss, VII cranial nerve palsy) [4], and the ICA [36]. Inflammatory involvement of the cranial nerves 5th and 6th gives rise to the typical ensemble of symptoms that configures GS. Beyond the involvement of 5th and 6th cranial nerves, typically described in GS, in our case, we radiologically documented initial spread of the inflammatory process to the intrapetrous horizontal tract of the ICA. The extension to the ICA represents a rare but potentially fatal complication, as well as a route by which the infection may spread to the neck through a periadventitial pathway, as previously reported by Somers et al. [36].

Once that AP has been identified, a therapeutic approach should be promptly established [10]. As for other potentially life-threatening infections, the antibiotic therapy must be immediately started upon an empirical, broad-spectrum approach. AP resulting from acute OM is frequently caused by Streptococci, Staphylococci, Pseudomonas species, *Haemophilus influenzae*, and Moraxella catarrhalis [4]. The setup of the empirical antibiotic therapy must take into account these species, and intravenous antibiotic therapy has to be performed, as recommended in the literature, from 2 to 9 weeks [5, 37]. Other very uncommon pathogens have been rarely reported in literature, i.e., fusobacterium spp. [13] or mycobacteria spp. [11] Tuberculous petrositis has been described mostly by reports from endemic areas. Its course is usually indolent and a scant and odorless otorrhea may be recorded for months [38]. Sensorineural hearing loss, facial palsy, tubercular meningitis, and tubercular cerebral abscess are possible complications [38]. Diagnosis of intracranial tubercular abscesses can be challenging and should take into account the immunological status of the patient (i.e., HIV infection should be investigated) and history of previous tubercular disease [38, 39]. Accurate imaging evaluation may differentiate tubercular from pyogenic abscesses (tubercular ones may have thicker walls and at MRI lower magnetic transfer of their wall is noted when compared with pyogenic abscesses). Certainly the presence of acid fast bacilli on a Ziehl-Neelsen staining or positive cultures of M. Tuberculosis is the gold standard for the diagnosis [39]. In these cases, a surgical approach is to be considered a first-line therapy, along with a long-term antituberculous therapy (> 12 months), that should be prolonged on the basis of the clinical and radiological course [11, 13, 39]. In our case, a causative pathogen could not be isolated from an auricular swab or blood culture. This may be due to the antibiotic therapy assumed by the patient prior to the admission to the hospital.

Historically, surgical therapy has been considered the treatment of choice in order to avoid the occurrence of further complications. This is confirmed by our review, which identified a high prevalence of patients referred to surgery, particularly when an apical abscess was present. However, the majority of those patients (50%) were treated with simple mastoidectomy or ventilation tube insertion, regardless of the presence of an abscess of the PA. On the contrary, direct apex drainage (DAD) surgery has been deployed only in 25% of the patients with abscess of the PA.

As a matter of fact, multiple reports of GS (regardless of the presence of an abscess) successfully treated with a conservative approach are currently available in the literature, thus limiting the role of surgery to patients with an insufficient response to a first-line antibiotic therapy or in critical conditions [5, 15, 37, 40, 41]. The trend towards conservative therapy is confirmed by Gadre and Chole's analysis upon the evolution of the treatments for AP. In their experience covering over 4 decades, a decrease of the cases treated with surgery was noticed, ranging from 50% in the 1970s to 12% of the cases occurred from 2001 to 2010. Moreover, in their case series, microbiologic cultures resulted positive in one-third of the cases, being *Pseudomonas aeruginosa* the most representative pathogen [4], thus underlining the importance of an accurately selected empirical antibiotic therapy. Whether the presence of an abscess within the PA may be relevant in determining the prognosis of the patient still remains controversial: the presence of an abscess of the PA was not even mentioned by some of the authors, even when evident by the radiological pictures, thus configuring a neglected entity. Moreover, it was not possible to correlate its presence with the necessity of aggressive treatment or with unfavorable outcomes, suggesting a limited role in the decision-making process in GS management.

In our report, surgical therapy was obviously discussed in a multidisciplinary setting comprising the pediatrician, the otoneurosurgeon with experience in lateral skull base surgery, the infectious disease specialist, and the neuroradiologist. Tympanostomy tube placement or simple mastoidectomy [4] was not considered in our case, in which a tympanic membrane perforation with active ear discharge was present, in the absence of clinical signs of acute mastoiditis. Other minimally invasive surgical approaches (such as mini craniotomy) were considered in order to obtain more purulent material for cultural analysis, but were reserved in case of insufficient response to the empirical therapy. Critical factors in determining a surgical approach to the PA include the hearing status of the

patient (hearing was preserved in our case), the size and location of the lesion within the petrous apex, and the neurovascular anatomy. If serviceable hearing is present, four main surgical approaches are considered: middle cranial fossa, endoscopic trans-sphenoidal, transcanal infracochlear, or infralabyrinthine [34]. The choice shall favor the shortest and least morbid route [4]. Overall, complications include damages to the meninges with cerebrospinal fluid leakage, bleeding from adjacent (possibly damaged by the infectious process) important vascular structures, otic capsule damage accidentally leading to postoperative vertigo or hearing loss, and facial nerve injury [34].

Since the spontaneous improvement of the patient, we decided to continue the antibiotic therapy with strict clinical follow-up, as summarized by Gadre and Chole in their management algorithm [4]. Follow-up imaging with MRI was performed to confirm the improving clinical trend, but its role was limited in the immediate decision-making process due to the need of a time course of at least 2 weeks for an appreciable improvement between two consecutive exams [4].

Conclusions

GS has been recently defined "the forgotten syndrome" [5]: the introduction of antibiotic therapy and the increased healthcare quality in the last century have turned an uncommon disease into a rarity [4]. This, in addition to the variability of the clinical picture of AP, usually defines a condition that is both potentially life-threatening for the patient and challenging to be recognized by the physician.

In the pre-antibiotic era, surgery was the only viable option for patients suffering from AP, but it carried also a great complications rate both in the intraoperative and postoperative course. The increased availability of powerful antimicrobial drugs in everyday clinical practice has profoundly changed this scenario, reserving surgery to those cases showing an insufficient response to medical therapy. For these reasons, after the first 24–48 h (considered critical in the surgical/conservative decision-making) [4], a strict follow-up remains mandatory. These fundamental moments shall involve a number of different healthcare specialists (namely the pediatrician, the otologist, the radiologist, the infectious diseases specialist, and the ophthalmologist) in a multidisciplinary setting.

Compliance with ethical standards

Conflict of interest None of the authors has any conflict of interest to disclose.

Ethics statement We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. Written informed consent was obtained from the patient's parents for publication of all clinical data, imaging, and pictures.

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