

Refractory Pseudomonas Osteomyelitis of the Skull Base With Gradenigo's Syndrome: Early Dysphagia and Late Abducens Nerve Palsy

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Abstract

Gradenigo's syndrome (GS) is a rare entity characterized by otitis media, pain in the trigeminal nerve distribution and abducens nerve palsy. The classic triad is uncommon, making the diagnostic workup challenging. Specifically, the diagnostic approach includes medical history, a complete otorhinolaryngological examination, a pure-tone audiogram and radiological investigation such as contrast-enhanced computed tomography scan and magnetic resonance imaging of head and neck. Broad-spectrum antibiotics are the first-line treatment, such as intravenous (IV) ceftriaxone and IV metronidazole. Here, we present the case of a 71-year-old man with a previous history of otitis media and poorly controlled type 2 diabetes mellitus. He presented to our attention with facial pain, left hemilarynx paralysis, dysphagia and otorrhea. The patient was treated with broad-spectrum antibiotics without any clinical improvement. Imaging evaluations demonstrated the presence of wide and poorly defined pathological material with epicenter in the masticatory space, involving all nearby structures. The patient underwent multiple biopsies without obtaining a definitive tissue diagnosis of neoplasia. After 2 months, the patient developed delayed VI cranial nerve palsy, providing evidence of GS. Although incomplete, GS has been described in the literature; however, none of the cases exhibited a latent abducent deficit. To the best of our knowledge, this is the only case with a delayed onset of abducens nerve palsy.

Keywords: Gradenigo's syndrome; Abducens nerve palsy; Otitis media; Skull base osteomyelitis

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Introduction

First described by Italian Otorhinolaryngologist Giuseppe Gradenigo in 1904 [1], Gradenigo's syndrome (GS) is a set of symptoms constituted by acute otitis media (AOM) with aural discharge, pain in the distribution of the trigeminal nerve and abducens nerve palsy [2]. Rare in the antibiotics era, GS is more frequently a consequence of petrous apicitis (PA), an intra-temporal and extracranial complications of suppurative chronic otitis media (COM). Complete presentation is uncommon (only 42% in the original series by Gradenigo) and is correlated with the extension in local structures as Dorello's canal and Meckel's cave, containing the abducens nerve and the cisternal trigeminal nerve. Deficits in other cranial nerves are rarer and correlate with skull base or cavernous sinus extension [3]. The recommended approach for treating this syndrome involves the extended use of intravenous (IV) antibiotics, bypassing surgical options such as mastoidectomy and labyrinthectomy. This preference is likely attributable to the intricate anatomy of the petrous apex air cells, necessitating precise surgical maneuvers in proximity to the surrounding labyrinth and carotid artery.

In this report, we present a case of elderly GS patient with unusual late presentation of abducens nerve palsy, making the initial diagnosis challenging in an already highly heterogeneous clinical entity. The aim of this report is to review all the diagnostic steps, including the encountered difficulties and considerations that made this diagnosis particularly arduous, and to assist future clinicians facing a similar situation with our experience.

Case Report

Investigations

A 71-year-old man was admitted to the Department of Emergency and Acceptation of San Camillo Forlanini Hospital in Rome, Italy, complaining of left COM with severe otalgia, otorrhea and recent onset of dysphonia, complete dysphagia, facial pain and body weight loss. COM had been present for 9 months, and 3 months before admission to our department, the patient underwent a canal wall up mastoidectomy at another

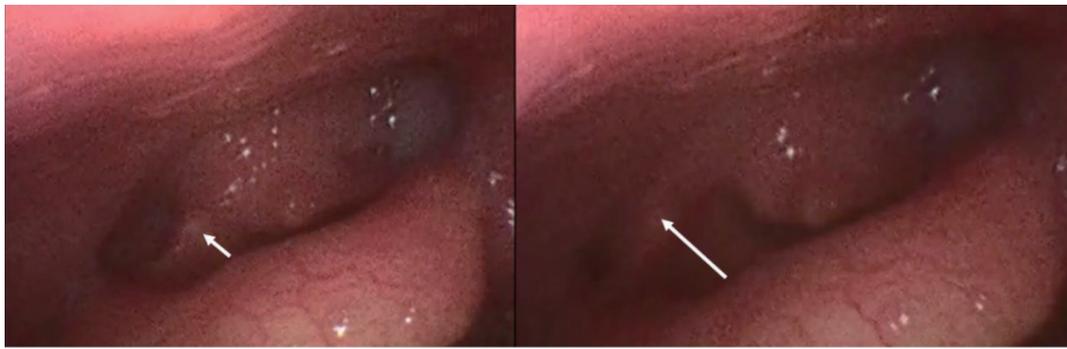


Figure 1. Complete left hemilarynx paralysis. During phonation, the correct motility of the right arytenoid cartilage is visible (white arrow).

hospital, without any benefit. His medical history was positive for poorly controlled type 2 diabetes mellitus and high blood pressure. Upon objective examination, the patient presented with a swelling involving the left parotid gland extending to the ipsilateral lateral cervical region. An upper airway evaluation with flexible fiber-optic laryngoscopy revealed complete left hemilarynx paralysis (Fig. 1). Otoscopy revealed a left side otorrhea, necessitating cleaning of the ear canal. An ear swab was performed, resulting in a positive test for *Pseudomonas aeruginosa*. Blood examinations showed high white blood cell count ($19.08 \times 10^3/\mu\text{L}$) with elevated inflammatory marker (C-reactive protein 6.05 mg/dL) and high glucose level (155 mg/dL). Consequently, the patient was treated with broad-spectrum antibiotics (IV ceftriaxone and IV metronidazole) for a duration of 6 weeks, without any clinical improvement.

Diagnosis

A magnetic resonance imaging (MRI) with contrast scan demonstrated the presence of wide and poorly defined pathological material (about $5 \times 6 \times 5$ cm) with epicenter in the masticatory space, involving all nearby structures (petrous apex, temporomandibular joint, oval foramen, Meckel's cave, middle

cranial fossa pachymeninges, sphenoid body and ipsilateral pterygoid apophysis, ipsilateral basisphenoid-basioccipital and hypoglossal canal, jugular foramen with internal jugular vein thrombosis, stylomastoid foramen, occipitomastoid fissure), indissociable from the deep side of the parotid gland. This lesion completely surrounded the internal carotid artery in the cervical-petrous passage, resulting in infiltrating stenosis. Computed tomography (CT) showed ipsilateral infiltration and erosions are noted on the clivus and petrous apex (Figs. 2-4). Given the inefficacy of the previous antibiotic therapy, and considering the difficulty in performing a radiological diagnosis and the strong suspicious of malignancy, the patient underwent periodic auricular toilets and multiple biopsies (nasopharynx, oropharynx, epiglottic vallecula, masticatory space) without obtaining a definitive tissue diagnosis of neoplasia. After 2 months the patient developed delayed VI cranial nerve palsy (Fig. 5), providing evidence of GS.

Treatment

The patient began systemic treatment with IV beta-lactam antibiotic (meropenem), three times a day for 6 weeks, as indicated by the infectious disease specialist. Due to the com-

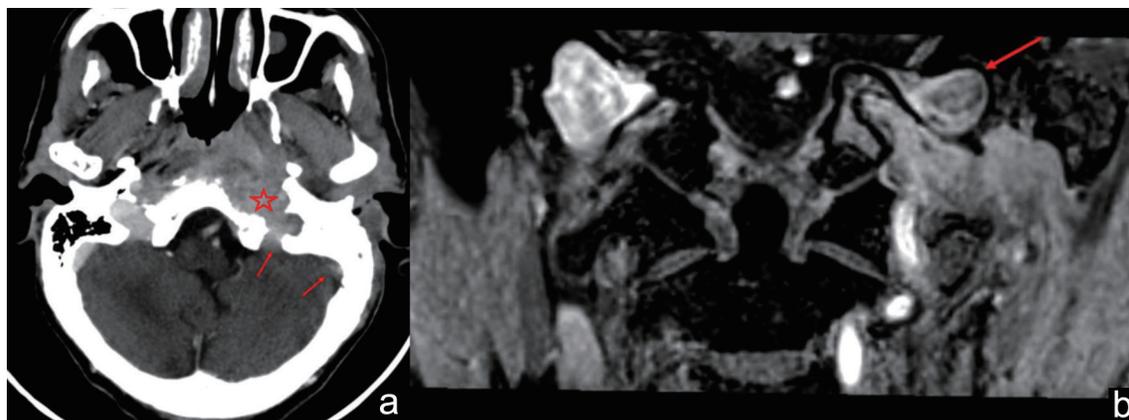


Figure 2. (a) Computed tomography (CT) scan after the administration of contrast medium shows thrombosis of the sigmoid sinus and jugular bulb (red arrows), which is inseparable from the pathological tissue (red star). (b) Magnetic resonance imaging (MRI) coronal T1w image after gadolinium administration. Thrombosis of jugular bulb (red arrow).

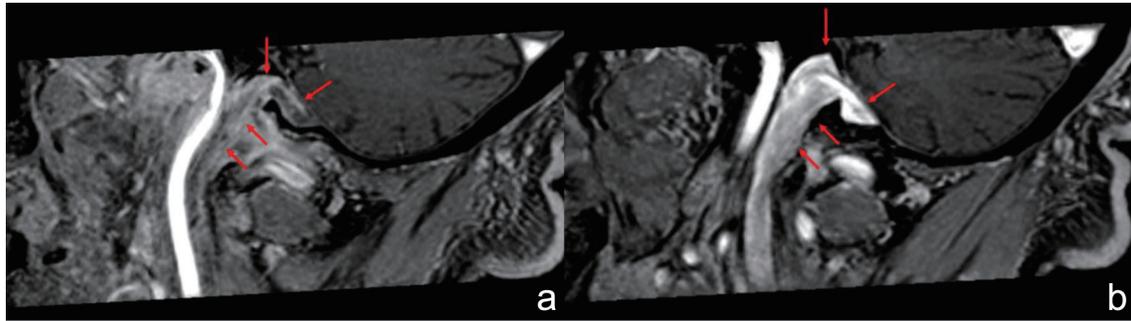


Figure 3. Magnetic resonance imaging (MRI) sagittal T1w image after gadolinium administration. (a) Thrombosis of sigmoid sinus and internal jugular vein (red arrows). (b) Right normal side, demonstrating normal appearance of sigmoid sinus and internal jugular vein (red arrows).

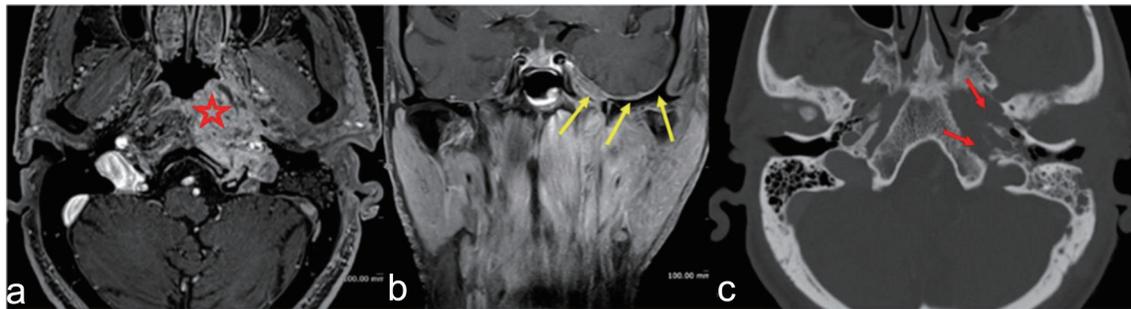


Figure 4. Magnetic resonance images in contrast-enhanced sequences, axial (a) and coronal (b). Axial cut in computed tomography (CT) (c). Infiltrative soft tissue mass in the deep spaces of the suprahyoid neck deforms the nasopharynx (red star); ipsilateral infiltration and erosion are noted on the clivus and petrous apex (red arrows). Pathological tissue extends to the oval foramen; dural thickening and enhancement on the middle cranial fossa floor and Meckel's fossa are appreciated (yellow arrows).

plete internal carotid involvement in the cervical-petrous tract, with secondary stenosis and the presence of internal jugular vein thrombosis, the patient presented a high anesthetic risk, contraindicating more invasive procedures. After 6 weeks of treatment, the patient's clinical and radiological condition improved despite residual neurological defects. He was discharged with oral quinolone antibiotic for 6 months and began speech rehabilitation.

Follow-up and outcomes

Patient is currently at a 12-month follow-up and his clinical

conditions are stable. Despite the decreasing percentage in recent years of isolated strains of *Pseudomonas aeruginosa* resistant to the main classes of antibiotics, there is still significant ciprofloxacin resistance in the intensive care setting. The use of beta-lactams and their effectiveness has allowed us to make a histological diagnosis *ex adiuvantibus* of skull base osteomyelitis, at the base of the GS.

Discussion

This case illustrates the complexity clinicians face in arriving at the correct diagnosis when dealing with GS that has diverse



Figure 5. Left abducens nerve palsy.

underlying etiologies, especially when the symptoms do not occur in a temporal order described in the scientific literature and when there is no response to initial therapeutic treatment, as in our case. Furthermore, complicating the situation is the patient's medical history, which included type 2 diabetes mellitus, COM and a previous canal wall up mastoidectomy without improvement of the infectious condition.

PA, an inflammation of the petrous apex of the temporal bone, can be considered as the typical feature of GS. A recent systematic review identified 134 patients with PA, of whom only 28 (20.9%) had the classic GS triad of abducens palsy, otorrhea, and retro-orbital or facial pain [4]. A male predominance of the disease is reported in literature with the age of patients ranging from 4 to 82 (mean age of 33 years) [3-5]. The etiology of GS results from PA secondary to multiple disease like AOM [6], COM [7] and extradural inflammation at petrous apex involving trigeminal ganglion and abducens nerve [2]. A predisposing factor of PA may be the degree of petrous apex pneumatization [8]. In most cases, infections are caused by pyogenic bacteria [9] as *Pseudomonas aeruginosa*, *Staphylococcus*, group A *Streptococcus* and *Klebsiella pneumoniae* [7], although atypical forms are described like two tubercular petrositis [10], two by *Fusobacterium necrophorum* [6], one by nontuberculous *Mycobacteria* [9, 10], and two by *Candida parapsilosis* [11, 12]. In addition, some authors have described a case of GS resulting from OM with effusion [13]. Patients often do not have the full triad but can develop it if the infectious condition is not treated properly [14]. Only 13-42% of patients develop the classic symptomatic triad [15, 16]. In some cases, it is masked by antibiotic therapy that targets specific organisms [17]. Photophobia and recurrent episodes of acquired esotropia with concurrent OM are reported in pediatric population [16, 18]. In children, the only PA symptom can be a long-lasting headache [19]. A recent classification proposal has divided the diagnostic categories of GS into three groups: classic presentation with evidence of PA, abducens nerve palsy, OM and trigeminal nerve pain; incomplete presentation with evidence of PA, abducens nerve palsy and OM or trigeminal nerve pain; mimic presentation without evidence of PA and abducens nerve palsy and OM or trigeminal nerve pain [20]. The possible spread infection to nearby structures can generate heterogeneous complications as meningitis, intracranial abscess, involvement of IX, X, XI cranial nerves (Vernet's syndrome) [21], prevertebral/parapharyngeal abscess, palsy, ipsilateral septic cavernous sinus thrombosis, cerebral venous sinus thrombosis, infectious arteritis of the internal carotid artery, carotid canal bone erosion, involvement of the jugular foramen and extension to sympathetic plexus with Horner's syndrome [1, 2, 11, 22-24]. The wide variety of clinical presentation can represent a challenge for physicians and lead to a wrong diagnosis. In the literature, right temporal headache and right retro-orbital pain were initially diagnosed as subdural hemorrhage [3]. A positive lumbar puncture for non-typeable *Hemophilus influenzae* led to a misdiagnosis of bacterial meningitis [17]. In patients presenting with the classic triad, the differential diagnosis should be made with Tolosa-Hunt syndrome and idiopathic chronic granulomatous inflammatory processes, commonly involving the cavernous sinus and the orbit, solitary osseous plasmacytoma of the skull base,

parapharyngeal rhabdomyosarcoma, T-cell lymphoma and undifferentiated nasopharyngeal carcinoma [21, 25-31]. Other mimicking GS etiologies are vascular trauma, cholesteatoma, Lemierre's syndrome, neuroblastoma, protein S deficiency, undifferentiated malignant round cell tumor and IgG4-related disease [20, 32]. Systemic lupus erythematosus may be a predisposing condition [30].

CT is a fast, sensitive and widely available exam. However, MRI is more specific for detecting involvement of petrous apex structures such as nerves, possible underlying osteomyelitis, neoplasms, and meningitis [33, 34]. A hypointense signal on a T1-weighted image and a hyperintense T2-weighted image with/without an enhancement edge are signs of PA on MRI. Imaging should include venous CT or MRI venography to exclude cerebral venous thrombosis [35]. Gallium-67 scintigraphy scanning can be performed to evaluate disease progression and treatment response [8].

Because of its rarity and clinical variety, the treatment of GS is still controversial. The need for medical therapy is undeniable; however, for further treatments it is necessary to evaluate case by case based on the patient and disease factors [36]. Etiology secondary to infectious processes requires long-term broad-spectrum antibiotics [3], in particular in cases of abscesses located in regions that are difficult to reach surgically due to surgical limitations or possible sequelae related to surgery [37]. Best clinical outcomes seem to be in those patients subjected to only medical therapy [8]. British guidelines of acute mastoiditis suggest as first therapeutic approach IV ceftriaxone + IV metronidazole. Moreover, for some authors traditional management of GS requires aggressive and radical surgery without any attempt to preserve hearing, especially for severe cases [3, 38]. The heterogeneity of presentation and involved districts determines a rich variability of suggested surgical approaches as craniotomy, trans cochlear approach, intact canal wall mastoidectomy with myringotomy and tube placement, simple ventilation tube insertion, infralabyrinthine approach between posterior semicircular canal and the jugular bulb, cortical mastoidectomy and myringotomy/grommet [16, 36, 38].

An elderly patient's peculiarity [5, 14, 39-41] is the presence of neurological defect, usually diplopia that correlates with Dorello's canal involvement developing in the early stages. Coexistence of predisposing conditions includes diseases like diabetes mellitus [29, 37] and immunodeficiency [11].

Only one case with previous radical mastoidectomy is reported [41]. To the best of our knowledge, this is the first case of GS described in the literature with a delayed presentation of abducens nerve palsy.

Learning points

In this report, we present a case of elderly GS patient with unusual late presentation of abducens nerve palsy. Data on the best diagnostic and therapeutic process of GS that can be used as guidance by physicians are limited, and further scientific evidence needs to be collected. The issue of antibiotic resistance is far from being solved, and greater efforts should be made to avoid unnecessary prescriptions. This study aims to highlight

the complexity of GS and stimulate scientific debate within the medical community.

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Financial Disclosure

None to declare.

Conflict of Interest

None to declare.

Informed Consent

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

Author Contributions

FM, AL, FC, and GV: conceptualization, creation of the initial draft, review of literature; AS: creation of the initial draft, review of literature; SDG and GB: revisions and final approval.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon reasonable request.

Abbreviations

AOM: acute otitis media; COM: chronic otitis media; CT: computed tomography; ENT: ear, nose and throat; GS: Gradenigo's syndrome; IV: intravenous; MRI: magnetic resonance imaging; OM: otitis media; PA: petrous apicitis

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