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Case Report

Stenotrophomonas skull base osteomyelitis presenting as necrotizing otitis externa: Unmasking by CT and MRI—case report and review

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ABSTRACT

Necrotizing or malignant otitis externa in patients presenting with mild clinical findings can pose as a tip of the iceberg; computed tomography (CT) and/or magnetic resonance imaging (MRI) unveils the clinical-imaging discrepancy and unmasks the presence of skull-base osteomyelitis (SBO). *Pseudomonas aeruginosa* is the most common causative pathogen of SBO, followed by fungal and other rare bacterial organisms. This report presents a rare case in an elderly diabetic patient, where the pathogen *Stenotrophomonas maltophilia* was isolated. There have been no previous reported cases in the literature of SBO caused by this pathogen. The hallmark of SBO on computed tomography or magnetic resonance imaging is soft tissue inflammatory changes under the central skull base with associated bone erosion. This may result in the peculiar appearance of the "Ovoid Gap" sign. SBO can be due to nonotogenic sources, namely: sinogenic, rhinogenic, pharnygogenic, or odontogenic infections. Low threshold for imaging is advised in immunosuppressed and elderly diabetic patients.

Background and introduction

Skull-base osteomyelitis (SBO), closely linked to necrotizing otitis externa (NOE), is a serious infection that is usually refractory to therapy. The term of "necrotizing otitis externa" is preferred than "malignant otitis externa". SBO follows a relatively indolent but complicated course given the risk of skull-base neurovascular involvement and intracranial extension [1–3]. The clinical significance is 2-fold: (a) an early clinical-imaging discrepancy, due to mild clinical presentation, leading to a delay in cross-sectional imaging which is the key to reveal skull base disease; (b) it can easily be confused with malignancy on imaging, causing delay in correct

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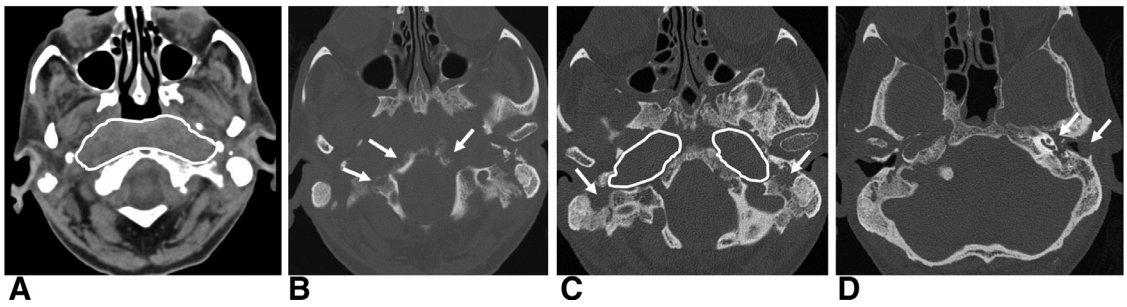

Fig. 1 – Axial CT soft tissues (A) and High resolution Temporal bone images (B-D). Confluent inflammatory prevertebral and posterior nasopharyngeal soft tissue thickening along the skull-base (A-white contours). Central skull-base erosion of petrous and occipital bones (B-arrows). Note erosive holes in inferior mastoid temporal bones (C-arrows). Bilateral "Ovoid" appearing gap between the bones at the central skull-base due to expansile and erosive soft tissue thickening (C-white contours). Left otomastoid and external ear nonerosive opacification (D-arrows).

diagnosis of SBO and, also leading to repeated biopsy attempts in search of malignancy. It is seen in immunocompromised patients, typically diabetic patients. Diabetes is itself a poor prognostic factor along with other factors like older age (>70 years) and a positive computed tomography (CT) scan [4,5]. SBO is most commonly of otogenic origin. This is due to an extension of NOE. Lateral infection in the ear may be trivial or not clinically apparent. SBO can also be of sinogenic, rhinogenic, odontogenic, or pharyngogenic origin. Nonotogenic SBO is distinguished by the term "central/atypical SBO" [1]. The prognosis tends to be very poor if adequate and appropriate antibiotic therapy is not administered from an early stage.

The clinical concepts of SBO and NOE were formalized in the 1950s and 1960s [2,6]. Most cases are thought to occur in elderly and diabetic patients, while younger patients can develop susceptibility due to immunosuppression. An inpatient study of 8300 patients has shown, however, that only approximately 23% of cases were in elderly diabetics [7], and recent evidence has even reported diagnosis in immunocompetent patients [8]. Patients with SBO and NOE initially present with otogenic symptoms and signs; the most common symptom being severe ear pain. The presentation of central or atypical SBO, on the other hand, is dominated by headache, facial pain, and cranial neuropathies.

Pseudomonas aeruginosa is the most common pathogen, however, there has been an increase in incidence of other pathogens (*Aspergillus spp*, *Staphylococcus aureus, Klebsiella oxytoca*) [1]. However, NOE due to *Stenotrophomonas maltophilia* is rare with very few reported cases [9], and there have been no reported cases of SBO caused by this pathogen within the English medical literature. This gram-negative bacterium is a nosocomial opportunistic pathogen that has the potential to cause fulminant septicemia in immunosuppressed patients. It can also harbor significant drug resistance [10]. The incidence is on the rise; it is usually isolated from polymicrobial respiratory tract infections, where it cocolonizes with *P. aeruginosa* [11]. Originally, it was named *Pseudomonas maltophilia* and then later classified in the genus *Stenotrophomonas* [12].

This report documents the first recorded case of biopsy and culture proven SBO caused by *S.s maltophilia*. This was in a diabetic patient presenting with mild otologic clinical stigmata. CT and magnetic resonance imaging (MRI) unmasked the depth of the iceberg in the form of typical skull-base bone erosion, with subtemporal and subclival inflammatory changes involving the prevertebral and nasopharyngeal submucosal soft tissues. The "Ovoid Gap" sign, due to medial subtemporal expansile inflammatory soft tissues, is emphasized on CT, along with the risk of carotid involvement (a risk factor for ischemic strokes).

Case report

An 82-year-old local male patient presented with a 1-month history of worsening headache, bilateral ear pain, and ear discharge on the left side. Past medical history was significant for diabetes mellitus, hypertension, chronic kidney disease, and treated rectal cancer. Diabetes mellitus was controlled with 3 medications. Physical examination showed mild left-sided ear discharge and bilateral tympanic membrane hyperemia. The clinical diagnosis was bilateral otitis media and left side otitis externa. Antibiotic therapy was immediately started.

After approximately 1 week, the left-sided ear discharge had resolved. However, due to persistent pain, bilateral myringotomies were performed for otitis media. Left-sided ear pain persisted. Physical exam showed a dry ear with no obvious cause for persistent symptoms. Inflammatory markers (eg, CRP) were high. Therefore, high resolution CT temporal bone (HR CT T-Bone) was performed. CT showed confluent soft tissue thickening along the central skull-base in the preclival nasopharyngeal and peridental soft tissue (Fig. 1A). Bone images revealed bone erosive changes along the inferior margins of the skull base (Fig. 1B and C). A peculiar "Ovoid Gap" appearance or sign was demonstrated at the skull base by virtue of remodeled-eroded margins along the expanded inflammatory soft tissue thickening (Fig. 1C). Bilateral inferior mastoid holes-like erosions were evident as well (Fig. 1D), in addition to nonspecific routine findings of bilateral nonerosive otomastoid opacification plus left external canal opacification (Fig. 1D). Findings were highly suggestive of type 2 SBO (NOE followed by SBO) with cross-extension. However, malignancy was needed to be excluded.

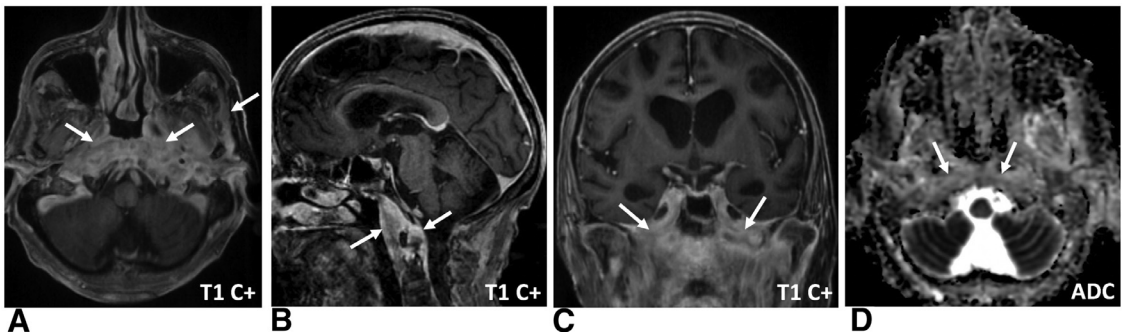

Fig. 2 – Axial (A), Sagittal (B), Coronal (C) contrast enhanced T1 and ADC maps skull-base. Diffuse crossed diffuse enhancing soft tissue thickening (A-C-arrows) in the preclival, posterior nasopharyngeal, upper parapharyngeal soft tissues under the skull base as well as left masticator space (A-left lateral arrow) and peridental involvement (B-arrows). Note facilitated diffusion on ADC maps (D-arrows) favoring inflammation against hypercellularity (of neoplasm) and excluding focal abscess.

MR imaging with contrast enhancement confirmed the soft tissue inflammatory process with better demonstration of the extent of the process (Fig. 2) including involvement of the left masticator space (Fig. 2A). Facilitated diffusion on the Apparent diffusion coefficient (ADC) maps (of diffusion-weighted imaging [DWI]) further supported the inflammatory nature of the process, rather than indicating malignancy (Fig. 2D). Input from the infectious diseases department recommended soft tissue, and, if possible, bone biopsy, to guide further management.

The patient was admitted to the hospital which was then followed by negative endoscopic evaluation. Deep nasopharyngeal soft tissue biopsy yielded chronic inflammatory changes with no malignancy, viral inclusions, or granulomas. PAS and GMS stains were negative for infective pathogens. Microbiology showed growth of *S.enotrophomonas maltophilia* sensitive to Ceftazidime, minocycline, and Trimethoprim. The patient was started on long term broad-spectrum intravenous antibiotics (IV Ceftazidime for 6 weeks). To date, the patient has shown clinical and imaging stability.

Discussion

Presented above is a smoldering case of SBO, preceded by a clinically benign appearing otogenic process, in an elderly diabetic patient. Cross-sectional imaging clearly manifested the rest of the "iceberg" with peculiar soft tissue bone erosive changes along the skull-base. *P. aeruginosa* as a pathogen, specifically in elderly diabetic patients, has typically been considered the sine qua non in NOE. However, other pathogens are being increasingly identified, including the unusual *S. maltophilia* as in this case report [9,13,14].

S. maltophilia, previously known as *P. maltophilia* or *Xanthomonas maltophilia* (now in a separate genus), is a commensal pathogen. It is a gram negative and nonfermenting aerobic bacterium that is already known to cause broad-spectrum infections, and it has recently also been associated with infectious pathology in immunocompetent patients. It is an environmental bacterium found in water, rhizospheres, animal microflora, and in foods. It has been isolated in a variety of infections including otitis externa [15], but it has never been recorded as the causative organism in SBO.

The pathophysiology of otogenic SBO is a result of the spread of infection from the external ear canal, along the temporal bone and through the fissures of Santorini at the osteocartilaginous junction. This leads to the risk of involvement of the cranial nerves and major vessels at the skull base. The inflammation extends under the temporal bone, with the potential to involve lateral structures and spaces including retrocondylar fat, temporomandibular joint, para-pharyngeal fat, and the masticator space. The spread pattern has been described as anterior (as above), medial (involving the nasopharyngeal and preclival soft tissues), crossed (with medial extension crossing the midline), and intracranial (bone erosive with paraclival extension into the middle and posterior cranial fossa). The disease thus progresses into SBO, which is described under 3 distinct types [16]:

(a) NOE with extension to the central skull base.
(b) Central SBO following resolved NOE.
(c) Central SBO as a primary or isolated presentation.

The case presented in this report best fits under the first type with crossed medial extension. CT, as a common first modality, may show nonspecific otomastoid changes or even a clear temporal bone. It is crucial to look for soft tissue inflammation under the skull base, as bone erosion may be subtle or even absent in the earlier stages. Diagnosis can be delayed up to approximately 2 months due to tricky clinical and imaging presentation [17]. Lateral soft tissues, along the petrous and basioccipital bones, can appear as the "Ovoid Sign" on bone windows, due to remodeled and eroded lateral bony margins by the expanded soft tissue inflammation (Fig. 1A). Authors have consistently observed this sign in cases of SBO. Significant foraminal erosion occur in the jugular foramen, carotid canal, and stylomastoid foramen. Contrast enhanced imaging can be helpful in the evaluation of carotid artery and jugular vein patency. As in this case, nasopharyngeal soft tissue thickening may be the most amenable site for sampling in order to

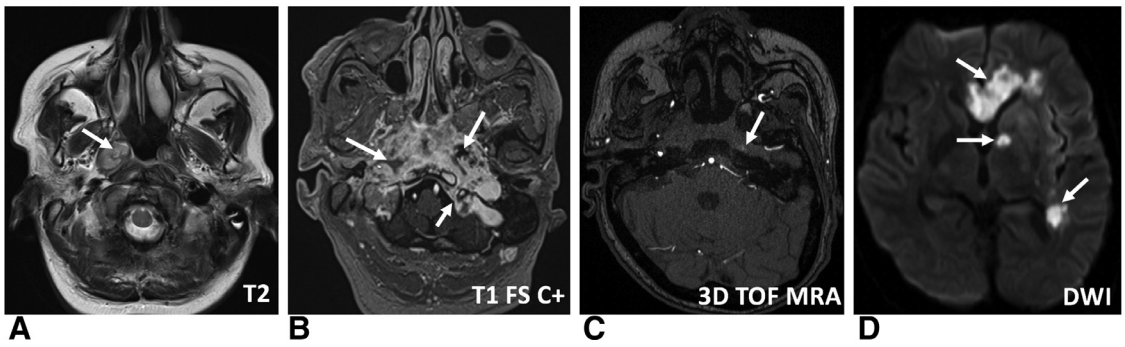

Fig. 3 – Axial T2 (A), fat saturated contrast enhanced T1(B), axial 3D TOF MRA source (C), and Diffusion weighted images (D). Initial isolated submucosal nasopharyngeal inflammatory focus (A-arrow) in a poorly controlled diabetic patient (other than the index case). Follow-up in few weeks show extensive crossed inflammatory soft tissue changes under the skull base with necrotic foci (B-anterior arrows). Note focal intracranial posterior fossa extension via bone erosion (B-small posterior arrow). Carotid sheath involvement with ICA encasement and eventual occlusion (C-arrow) and multiple acute embolic infarcts in ICA distribution.

rule-in SBO and rule-out malignancy. The process may even start in the pharynx (Fig. 3A). The second and third types of SBO usually present with cranial neuropathy, increased erythrocyte sedimentation rate, and abnormal clival findings [18].

MRI imaging complements the findings on CT. MRI is more helpful in detecting intracranial extension of the disease whether it may be direct, perineural, or vascular. Contrast enhanced study is helpful in delineating necrotic changes (Fig. 3B). Involvement of the major skull base foramina can be better assessed on MRI. One of the serious complications is internal carotid encasement resulting in steno-occlusive disease and ischemic strokes (Fig. 3C and D) [19].

The major differential diagnosis for SBO includes nasopharyngeal carcinoma, head and neck squamous cell carcinoma, lymphoma, and metastases. The findings of SBO are nonspecific, and this accounts for the multiple biopsies usually taken in these patients. Clinical input may not be helpful in the early course of the disease, unless there is a history of diabetes mellitus in an elderly patient (particularly if poorly controlled), or any other cause of immunosuppression in younger patients. Amongst advanced MRI techniques, DWI can be helpful in differentiation between lymphoma/nasopharyngeal carcinoma and bacterial SBO [2]. ADC values in malignant neoplastic disease tend to be reduced mainly due to relative hypercellularity. Higher ADC values are expected in bacterial SBO (Fig. 2D) unless there is focal abscess formation which typically shows restricted diffusion. For skull-base evaluation, nonecho planar DWI is preferred to reduce susceptibility artifacts.

Nuclear Medicine imaging can provide helpful diagnostic tools in the early detection of SBO, and can add specificity to the findings on CT and MRI in more challenging cases [1,2]. More important is the role of monitoring the response to therapy. Tc99 bone scan use is limited due to nonspecificity. Leukocyte scan (Tc99) is the nuclear medicine scan of choice and preferred over GA-67 among gamma ray tracers. The use of FDG-PET scan as beta emitting tracer imaging is also limited by specificity as a malignant neoplasm will show uptake. However, FDG-PET is useful in delineating the extent of the disease and the response to therapy.

The mainstay of therapy for SBO is long-term intravenous broad-spectrum antibiotic treatment. Complete response to treatment can take several months. Surgery is rarely needed for removal of inflammatory sequestra. Early and effective treatment means better prognosis, reduced neurologic sequela, and decreased mortality. Older age and immunosuppression play key roles in the prognosis of the patient. Therapy alone will not help with out optimal control of diabetes and immunosuppression [1,3,20]. Antibiotic therapy has resulted in improved prognosis. Johnson et al showed patient survival of up to 90% at a mean of 18 months follow-up, with residual neurological disability and overall mortality in approximately 30% and 10%, respectively [3]. Prognosis is worse for patients >70 years old with a 5-year survival of approximately 44% compared to approximately 75% in younger patients [21–24]. Mortality can be attributed to multiple factors, mainly: (a) systemic immunosuppression (including nondiabetic patients); (b) diabetic factors; and (c) local invasive factors (specifically local meningeal or parenchymal invasion, vascular involvement of carotid arteries causing localized vasculitis, ischemic embolic strokes, and the dreaded complication of mycotic aneurysms). Vascular skull base involvement can result in dural venous thrombosis which can include the cavernous sinuses.

Summary

SBO is a serious sequela of necrotizing/malignant otitis externa and warrants focused evaluation of skull base soft tissues with associated erosive changes on cross-sectional imaging. Resultant peculiar “Ovoid Gap” sign may be observed between the skull base bones. Nonotogenic infection can cause SBO as well, which is described as “central or atypical SBO”. Most of these patients tend to be elderly diabetics and

low clinical suspicion of deeper infiltrative disease. Causative pathogens other than *P. aeruginosa* are being identified (such as *S. maltophilia* as in this case). Prognosis is very poor in cases where antibiotic therapy is delayed.

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