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Case report

Central skull base osteomyelitis secondary to invasive aspergillus sphenoid sinusitis presenting with isolated 12th nerve palsy

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ABSTRACT

Skull base osteomyelitis is a potentially life-threatening infection, usually seen in elderly immunocompromised patients secondary to malignant otitis externa (MOE) caused by *Pseudomonas*. Central or atypical skull base osteomyelitis often poses a diagnostic challenge as they present as head-ache with or without cranial nerve palsy often without any obvious source of infection. Although the incidence of fungal skull base osteomyelitis is increasing central skull base osteomyelitis due to invasive fungal sinusitis presenting with isolated hypoglossal nerve palsy has not been reported in the literature, to our knowledge. We report a case of a 59-year-old diabetic patient on regular treatment including steroid for acetylcholine receptor binding antibody positive myasthenia gravis with thymoma who presented with persistent head-ache and on evaluation, was found to have 12th cranial nerve palsy on the right side. She was diagnosed to have invasive fungal sphenoid sinusitis and central skull base osteomyelitis involving the clivus and was successfully treated with endoscopic transnasal transsphenoidal debridement followed by antifungal therapy.

Introduction

Skull base osteomyelitis (SBO) is a rare, but grave infection with significant mortality and morbidity if not recognized and intervened on time. The inflammation of the skull base results from infection from neighbouring tissues like ear or paranasal sinuses infection. It usually affects elderly diabetic immunocompromised patients, typically as a complication of malignant otitis externa (MOE). While MOE primarily affects the temporal bone, central or atypical SBO can be seen affecting the sphenoid and occipital bone, often centered on the clivus [1].

Sie et al. first reported atypical or central SBO in patients without otitis externa or any other contiguous infection [2]. Here we report a similar case of skull base osteomyelitis which occurred as a complication of sphenoid sinusitis rather than MOE, caused by invasive *Aspergillus* infection, with isolated hypoglossal nerve palsy.

The most common presenting symptom in these patients is deep-seated pain [3]. The diagnostic dilemma in skull base osteomyelitis cases occurs when most patients present with pain and cranial nerve involvement with no obvious infectious source and thereby giving a high suspicion of malignancy. The crux of management lies in the accurate histological diagnosis as the imaging findings frequently mimic malignancy [1]. Nonetheless, it is one of the rare instances when cranial nerve palsies can be seen to recover completely if diagnosed and treated appropriately.

A high index of suspicion, early diagnosis, identification of the causative pathogen(s), prompt initiation of appropriate antimicrobial or surgical therapy, the reversal of immunocompromised state wherever possible, and continuation of therapy for an adequate period are essential when managing SBO. Identification of the pathogen often requires a surgical biopsy, but this may be delayed for medical or technical reasons. So, clinical features or risk factors that differentiate between SBO caused by bacteria and that due to fungi can guide the selection of empiric antimicrobial therapy [4].

CASE REPORT

A 59-year-old lady with a history of diabetes mellitus on poor glycemic control for the last 20 years and thymoma with Acetylcholine receptor binding antibody positive myasthenia gravis on regular treatment for the past one year was referred to our department from the neurology department with complaints of persistent headache of 8 months duration. She was also noticed to have a history of slurring of speech of 1-week duration at the time of presentation.

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Examination revealed thyroid swelling, acro-oral vitiligo and hirsuitism. She was also having bilateral partial ptosis as part of myasthenia gravis. Ear examination was completely normal with no features of otitis externa. Nose examination was also normal except for bilateral inferior turbinate hypertrophy and there was no paranasal sinus tenderness. She was observed to have a deviation of tongue to the right side with fasciculation suggestive of right 12th cranial nerve palsy. The rest of the system examination was normal.

Routine blood investigations were within normal limits except for raised ESR of 82 mm/hr, CRP- 14.5 mg/L and HbA1c -11.

CT paranasal sinus showed sclerotic changes involving the body of sphenoid, greater wing, clivus, bilateral squamous temporal bone, and petrous apex with soft tissue density with calcification in right sphenoid (Fig. 1). MRI brain showed a hypointense lesion involving the body of sphenoid (R > L) and clivus on T2 weighted images (Fig. 3) and T1 weighted images (Figs. 2 and 3) with moderate contrast enhancement possibly fungal in aetiology (Fig. 4).

She underwent endoscopic sphenoidotomy and debridement which showed unhealthy bone on right sphenoid posterior wall and clivus. The biopsy was taken from the unhealthy clival bone and sphenoid mucosa. Histopathology report revealed invasive fungal sinusitis morphologically *Aspergillus* with foci of tissue invasion.

She was treated with parenteral ceftazidime for 10 days till the histopathology reports were available, followed by oral voriconazole for 10weeks and other supportive measures including strict glycemic control. On follow-up, the patient was symptomatically better, with improvement in 12th cranial nerve palsy. She is under regular follow-up.

Discussion

Elderly, diabetic, immunocompromised predominantly male patients are mostly at risk [4]. According to Sreepada et al., in diabetes, there is defective chemotaxis and phagocytosis of polymorphonuclear leukocytes (PMNs), monocytes, and macrophages. The oxidative burst and killing function of PMNs are also shown to be reduced in diabetics predisposing them to infection [5].

Generally, they present with headache or deep-seated pain, often intractable, as the lone symptom, with complaints related to the individual cranial neuropathies occurring later [6]. Usually, multiple cranial nerves involvement is seen, especially the lower cranial nerves (IX, X, XI, XII), and if the involvement of cranial nerve VI along with this in particular, should raise the suspicion of clival pathology [1]. But, here our patient presented with isolated 12th cranial nerve palsy, which is a very rare presentation of skull base osteomyelitis.

The most common cause of isolated 12th cranial nerve palsy was found to be malignancy [7], followed by other rare causes like carotid artery aneurysms [8], vertebral artery dissection [9], cervical osteophytosis [10], calcified persistent hypoglossal artery [8], synovial cysts [9,12], vasculitis/rheumatological diseases, dental disease [10,13], trauma [11,14] and following transoral intubation [12,15].

Routine blood investigations generally reveal a normal picture except for the uncontrolled diabetic status and elevated acute phase reactants, especially ESR and CRP. This helps in differentiating between malignancy and skull base osteomyelitis, as it is unlikely to expect elevated acute phase reactants with malignancy. ESR and CRP monitoring is vital as its normalization would indicate the subsidence of infection and thus has an important role in defining the duration of treatment [1].

A variety of imaging modalities can be used for assessment of these patients and of these MRI is probably the most important. Even though MRI cannot detect bone destruction, the superior soft tissue discrimination is useful for analysing the soft tissue planes around the skull base and medullary cavity of the bone. The most common MR findings of osteomyelitis include marrow T1 hypointensity and T2 hyperintensity according to Chang et al. [16]. Clival enhancement can also be seen, but it poses a diagnostic challenge as it can be seen with neoplastic processes as well.

CT scan helps to evaluate the extent and severity of SBO by detecting bone erosion, but more than 30 % of affected bone should be demineralized before it is evident and hence, early findings are limited to soft tissue inflammation [5]. The major drawback of CT is that the changes fail to resolve for a long time after treatment is finished, so the use of it as a tool for follow-up is not advised [17].

So, both MRI and CT scan are complementary to each other and hence, both are advocated to get as much information as possible.

Other nuclear medicine imaging techniques like SPECT/CT with 67Gallium- or 111Indium -labelled WBCs help in improving the diagnosis, localization, or definition of the extent of disease [18]. Technetium-99 m methylene diphosphonate (MDP) bone scans, and single-photon emission computed tomography (SPECT) have an advantage in detecting postoperative osteomyelitis and plays an

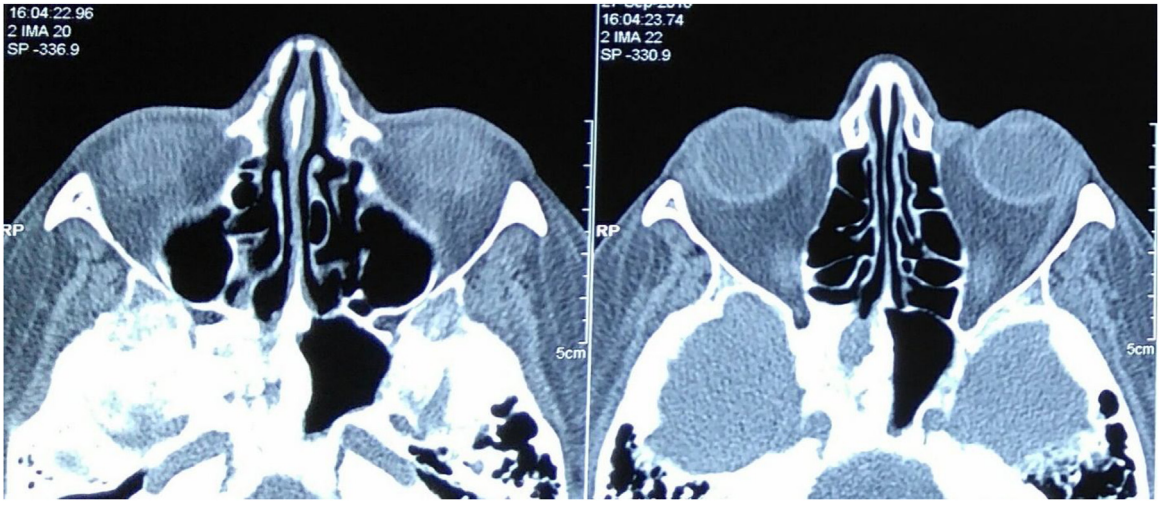
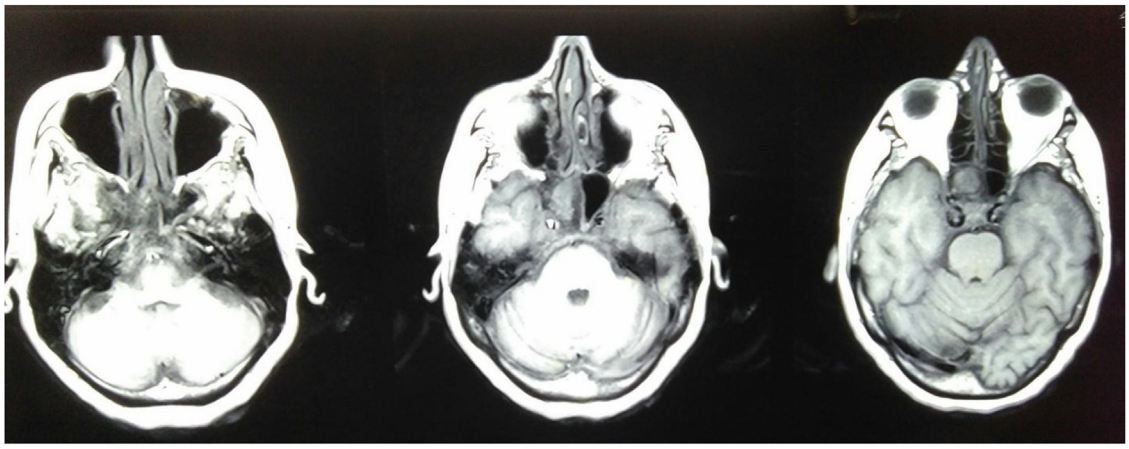
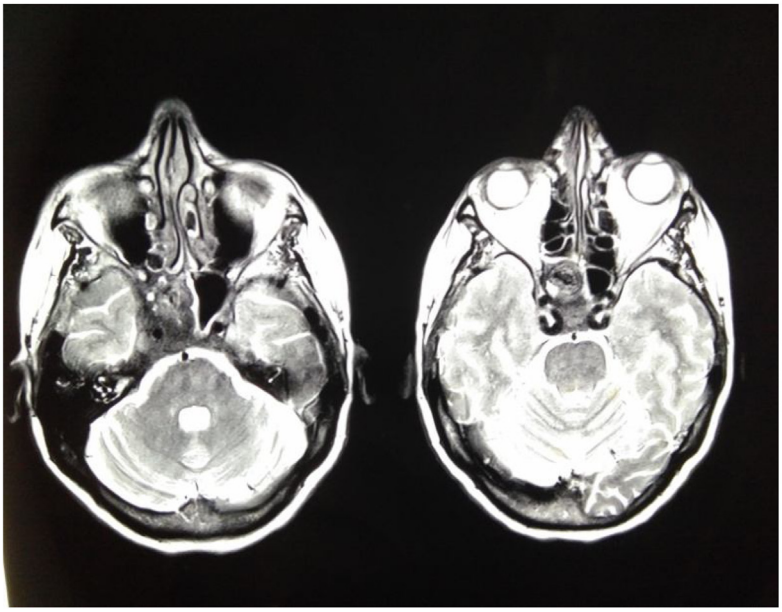


Fig. 1. Sclerotic changes involving body of sphenoid, greater wing of sphenoid, soft tissue density lesion with calcification in (R) sphenoid.





Figs. 2 and 3. MRI brain showing hypointense lesion involving body of sphenoid (R > L) and clivus on T2WI which was hypointense on T1WI.

important role in the follow-up of patients on antibiotics as marrow signal persists for up to 6 months after successful treatment [17].

Soft tissue swelling below the skull base and changes in petrous apex and/or basiocciput like the bone erosion and marrow infiltration typically point towards an underlying malignant process. So, it is mandatory to send biopsy material for histology as well as microbiological analysis (including fungal and mycobacterial cultures) and finally, this becomes the keystone for confirming the diagnosis and further planning of the treatment, especially about the antimicrobial regimen [1].

Pseudomonas aeruginosa is the most common pathogen implicated in osteomyelitis secondary to malignant otitis externa [19]. This seems true for central SBO also, although other organisms have been reported, including *Aspergillus* [20], Gram-positive organisms [8], mycobacterium, and *Candida* [16]. Fungal SBO has been reported to be mostly caused by *Aspergillus*, and less commonly, *Scedosporium* spp [20,21]. Although, underlying diabetes and primary or acquired immunodeficiencies have often been evident [22], fungal SBO has also occurred in the absence of these traditional risk factors.

Patients with fungal SBO were more likely to have underlying chronic sinus disease, symptoms attributable to invasive sinus infection (sinofacial pain, periorbital swelling, nasal stuffiness/discharge), but with a relative paucity of features attributable to ear infection. Indeed, the absence of purulent ear discharge was a sensitive (91 %) predictor of underlying fungal SBO [23].

The management of SBO should be dealt with a multidimensional approach. This approach includes prolonged culture guided antimicrobial therapy with control of underlying comorbid factors such as aggressive glycemic control in diabetes and improvements in immune status in immunocompromised patients [24]. The duration of antimicrobial therapy is variable among the cases reported, but in each case treatment is to be given for at least 1 month and up to 6 months or more.

The tissue uptake of antibiotics in bone is affected by vascularity and the presence of concomitant disease. Small vessel diseases especially in diabetes further compromise antibiotic uptake and affect tissues. Usually, chronic osteomyelitis is associated with necrotic bone and it is believed that the organism is not rapidly multiplying. Hence, it is necessary to obtain high levels of antibiotic over a prolonged period in the infected tissues [3].

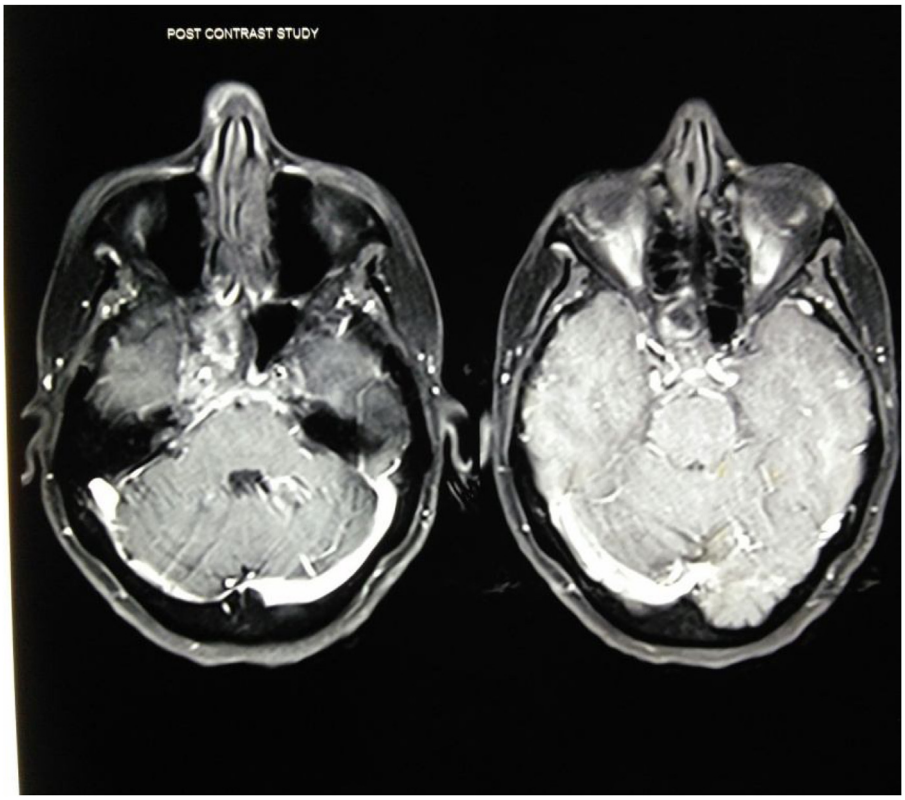


Fig. 4. MRI brain T1WI showing post-contrast enhancement.

The role of surgery is confined to biopsy, drainage of abscess if any [3], and removal of sequestra by surgical debridement. This helps in source reduction and decreased inflammatory load while improving the availability of antimicrobial agents to the affected region [24]. The tissue sample plays a vital role in substantiating the diagnosis of SBO by histopathology and microbiology to exclude malignancy.

As expected, amphotericin B is the drug most commonly used in the treatment of *Aspergillus* osteomyelitis, followed by two azoles: itraconazole and voriconazole. Echinocandins were only rarely used [25]. According to The Infectious Diseases Society of America guidelines, either amphotericin or voriconazole can be used for the treatment of *Aspergillus* osteomyelitis, whereas the British Infection Society recommends amphotericin in combination with flucytosine for severe cases and itraconazole for the treatment of stable patients [26]. Both itraconazole and voriconazole are less toxic than amphotericin B; also, they can be administered orally, and achieve bone concentrations above the typical MIC for *Aspergillus* [27]. The potential risk of complications include the cranial nerve palsies, meningitis, cerebral venous thrombosis, arterial infarcts and death [1,28]

Conclusion

Central skull base osteomyelitis is a rare, life threatening condition and that secondary to invasive aspergillosis presenting with isolated hypoglossal nerve palsy is extremely rare. Central skull base osteomyelitis is rare, and of this that secondary to invasive aspergillosis leading to isolated hypoglossal nerve palsy is very rare. Cranial nerve palsies in the elderly diabetic or immunocompromised patient, with imaging findings of a lesion causing bony destruction in the central skull base, should be dealt with a high index of suspicion. A systematic analysis of clinical features, imaging, inflammatory markers augmented with histological and microbiological assessment can only help us to reach the correct diagnosis. Early initiation of antibiotic/antifungal therapy is desirable to lower the risk of potential sequelae, which can prove to be fatal. The duration of treatment is guided by clinical findings, normalization of inflammatory markers, and resolution on the bone scan if available.

Hence a prompt intervention at the accurate time and commencement of appropriate treatment after identification of pathogen and continuation of therapy for an adequate period is the key in the management of skull base osteomyelitis.

CRediT authorship contribution statement

Suma Radhakrishnan: Conceptualisation, Data curation, Supervision, Writing - original draft, Writing - review & editing. **Hiba Mujeeb:** Writing - original draft. **Chandni Radhakrishnan:** Writing - review & editing.

Declaration of Competing Interest

The authors report no declarations of interest.

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