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OTOLOGY

Aspergillus infections of lateral skull base: a case series

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Abstract

Purpose While extensive research with accurate classification has been done in mycoses of the paranasal sinuses and anterior skull base, a similar understanding of lateral skull base fungal pathologies is lacking due to relative rarity and diagnostic difficulties. We introduce a series of eleven cases and two different invasive entities of *Aspergillus* temporal bone diseases—*fungal skull base osteomyelitis* (SBO)/*malignant otitis externa* (MOE) and *chronic invasive granulomatous fungal disease* (CIGFD).

Methodology A retrospective observational study was conducted at the neuro-otology unit of a tertiary care referral center between July 2017 and November 2022. Diagnosed cases of lateral skull base osteomyelitis with atypical symptoms and lack of response to culture-directed antibiotics were evaluated for fungal origin. Patient data, including history, laboratory findings, serum galactomannan assay, CT and MRI imaging findings, clinical examination findings, and co-morbidities, were analyzed. The treatment course and response were assessed.

Results A total of 11 cases were included in the study. Of these, 9 were cases of *Aspergillus*-induced skull base osteomyelitis (SBO) and 2 of *Aspergillus*-induced chronic invasive granulomatous fungal disease (CIGFD). CIGFD presented with persistent ear discharge and slowly progressive post-aural swelling, while all patients of fungal SBO had lower cranial nerve palsies. CIGFD responded to excision and antifungals, while SBO responded well to conservative anti-fungal treatment.

Conclusion In cases of lateral SBO not responding to antibiotic therapy, the possibility of fungal etiology should be considered. *Aspergillus* spp. seems to be the major fungal pathogen.

Keywords Aspergillus · Lateral skull base mycoses · Atypical skull base osteomyelitis · Galactomannan assay · Voriconazole · Granulomatous fungal disease · Invasive mycoses

Introduction

Members of the *Aspergillus* species are ubiquitous fungi primarily found in soil and decaying organic matter [1]. Given how universal they are, it is not surprising that *Aspergillus* is the most critically emerging fungal pathogen, causing a wide spectrum of human and animal infections ranging from superficial cutaneous infections to life-threatening invasive mycoses. In addition, the rising rates of diabetes mellitus, immunosuppressive therapies, and increasing life span of patients with conditions causing immunosuppression along with emerging viral diseases like COVID-19 make fungal infections an impending threat among infectious diseases [2].

The most common otological manifestation of *Aspergillus* infection is otomycosis [3]. It is a non-invasive form of saprophytic colonization of the external ear canal that can occur in both immunocompetent and immunocompromised individuals. Also, it is a very well-known condition among otorhinolaryngologists. The invasive forms should be discussed and understood more.

While extensive research with more accurate classification has been done in mycoses of the anterior skull base, a

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similar understanding of fungal pathologies of the lateral skull base is lacking. This is due to the relative rarity and diagnostic difficulties of these conditions.

The majority of the literature on temporal bone mycoses are one-off case reports [4]. Here, we introduce a series of eleven cases and classify them into two different invasive entities of *Aspergillus* temporal bone diseases—*fungal skull base osteomyelitis* (SBO)/*malignant otitis externa* (MOE) and *chronic invasive granulomatous fungal disease* (CIGFD). An attempt has been made to outline a diagnosis, management, and follow-up for these conditions. In addition, we discuss the other reported lateral skull base fungal entities and attempt a classification in lines of anterior skull base mycoses.

Materials and methods

A retrospective observational study was conducted at the neuro-otology unit of a tertiary care referral center between July 2017 and November 2022. The Institute Ethics Committee approved the study (IEC Code: 2022-148-IP-EXP-50). The Cohen and Friedman criteria were used to diagnose skull base osteomyelitis [5]. The clinical findings included severe otalgia, specifically nocturnal ear pain, edema, ear discharge, external auditory canal granulations, lower cranial nerve palsies, and positive radiological signs in either computed tomography (CT) or magnetic resonance (MRI) imaging, especially in the backdrop of uncontrolled diabetes mellitus. Pathologies like malignancy and cholesteatoma were ruled out by tissue biopsy of granulations or the samples obtained during surgery. The patients were treated with culture-directed antibiotics. Those not responding to appropriate antibiotic therapy, as evident by new onset symptoms/lower cranial nerve palsies or exacerbation of existing symptoms during antibiotic therapy, were assessed for the possibility of fungal etiology. A serum galactomannan assay of >0.5 or histopathology suggestive of *Aspergillus* was considered for starting anti-fungal therapy. Patient data, including history, laboratory findings, serum galactomannan assay, CT and MRI imaging findings, clinical examination findings, and co-morbidities, were noted and analyzed. The treatment course and response were assessed. Informed consent was obtained wherever appropriate.

Statistical analysis

The collected data were analyzed using a Microsoft Excel sheet and IBM SPSS Statistics Version 2.2 (Armonk NY; IBM Corp). Percentage and frequency were calculated for patients' demographic profiles and clinical and laboratory characteristics.

Results

A total of 11 cases were included in the study. Of these, 9 were cases of *Aspergillus*-induced skull base osteomyelitis (SBO) and 2 of *Aspergillus*-induced chronic invasive granulomatous fungal disease (CIGFD). The majority were male, with 8/9 in the SBO group and 1/2 in the CIGFD group. The mean age of patients with Aspergillus-associated lateral skull base osteomyelitis was 54.10 years {median 55 years, standard deviation (SD) 12.66}.

Clinical presentation

Chronic invasive granulomatous aspergillosis of the temporal bone—Both patients presented with a history of gradually progressive non-tender post-auricular swelling. One (female) patient, 31 years old, had a persistent post-auricular sinus and a history of four ear surgeries in view of recurrent ear discharge over a period of 9 years. The 29-year-old male patient had no other symptoms or examination findings, except hard of hearing on the affected side. The pure tone averages of 500, 1000, and 2000 kHz of patient 1 (female) was 55/80 (BC/AC) dBHL, and the second patient was 38/60 dBHL.

Aspergillus-associated skull base osteomyelitis (Table 1)—All the patients were initially diagnosed with lateral skull base osteomyelitis according to the Cohen and Friedman criteria, received appropriate antibiotic therapy, and were referred to us with persistent/ worsening clinical symptoms. The details of clinical symptoms and signs are given in Table 2. Cranial nerve involvement is one of the most common presentations among patients. The nerve most commonly involved was the facial nerve. Isolated facial nerve palsy was present in 3 patients (33.33%), and facial nerve palsy and other lower cranial nerve palsies were found in 5 patients (55.55%). On the other hand, one patient (11.11%) presented with lower cranial nerve palsies *without* facial nerve palsy (CN IX, X). Out of eight patients with facial nerve palsy, three (37.50%) presented with House Brackman Grade III, and four (50.00%) had Grade V palsy. One patient had a Grade VI palsy.

Comorbidities

Both the patients with CIGFD of lateral skull base were immunocompetent. 8 out of 9 patients with SBO had elevated blood sugar levels, with 7 (77.77%) non-insulin-dependent diabetes mellitus and 1 (11.11%) with insulin-dependent diabetes mellitus (IDDM). No other conditions causing immunosuppression were present.

Course of treatment

CIGFD: Both patients with CIGFD presented a diagnostic dilemma. In view of progressive mastoid/temporal area swelling in spite of antibiotic therapy, culture sensitivity, and biopsy were done to exclude temporal bone malignancy and invasive fungal disease. The culture was sterile in one case (male) and positive for *Pseudomonas* in the female patient, with no fungal elements, and the biopsy was initially inconclusive. So, a mastoid exploration was done including frozen section, histopathology, and maximum possible debulking of the lesion. Intra-operatively, the lesions were firm, fibrous, and gritty with limited vascularity. They were found to adhere firmly to the dura of the middle and posterior fossa in both cases. The lesions were shaved from the dura to avoid dural entry and CSF leak. In both cases, intra-operative frozen section confirmation of granulomatous lesion was received. Periodic acid–Schiff (PAS) staining was suggestive of septate fungal hyphae with occasional acute angle branching, and fungal culture showed growth of *Aspergillus* spp. after 05 days of incubation (Fig. 1).

Both patients completed 6 months of oral voriconazole therapy (Figs. 2 and 3).

Skull base osteomyelitis: Among the SBO group of patients, 5 patients (55.55%) presented with the typical external auditory canal (EAC) granulations and discharge, while 4 patients (44.44%) had normal tympanic membrane and EAC. Culture and sensitivity were positive for *Pseudomonas* in two patients and either sterile or not available due to the absence of pus in the rest of the patients. Tissue sampling was possible only in 5 patients, and only one showed thin hyaline septate fungal hyphae suggestive of Aspergillosis. All the patients had a serum galactomannan assay index of more than 0.5 and were managed with oral voriconazole 200 mg BD for 1 day (loading dose) followed by 100 mg BD for 3–6 months. Other symptomatic medications, like analgesics, were given on a case-to-case basis. The total length of treatment ranged from 3 to 6 months (mean 4.80 months, median 5.25 months, SD 1.40), and patients were followed up for 6–24 months (Fig. 4).

Follow-up

All the patients were followed up on a monthly basis, and their responses to treatment were noted. One patient with CIFGD completed three years of follow-up without evidence of recurrence or new onset of symptoms. The other patient completed 6 months of therapy with complete remission of the disease. All the patients with SBO were followed up with clinical reassessment, serum galactomannan assay

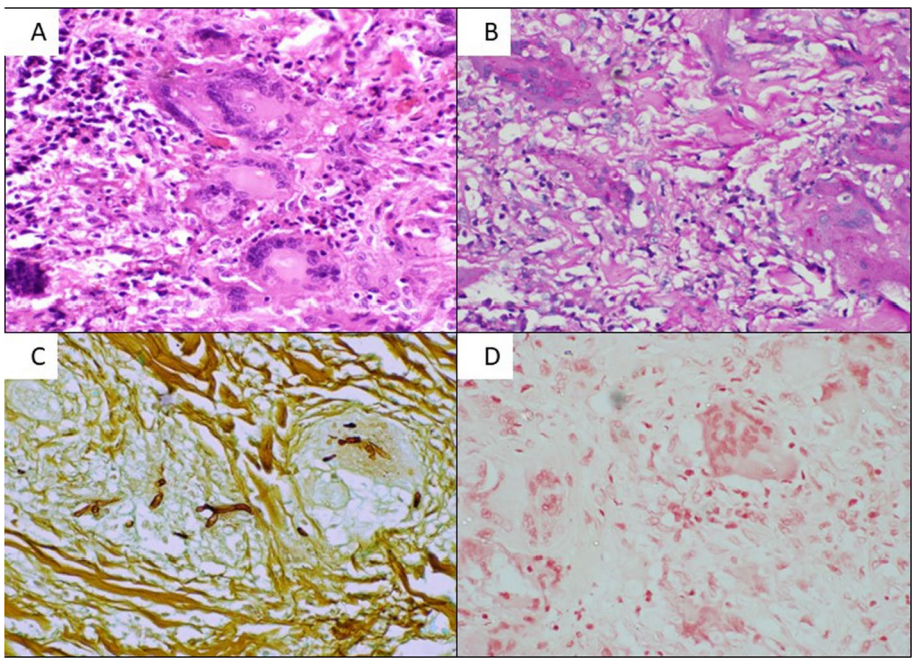

Fig. 1 Histopathology features of *Aspergillus*-related chronic granulomatous fungal disease. **A** The sections from post-auricular mass show fibro-collagenous tissue with multiple granulomas comprising multinucleated foreign body giant cells, histiocytes, lymphocytes, plasma cells, and eosinophils. **B** (PAS stain) and **C** (CSM stain). Many septate fungal hyphae with occasional acute angle branching are seen. Hyphal swelling is also seen. Microscopy for fungus: 10% KOH wet mount shows plenty of tissue debris, pus cells, and septate acute angle branching fungal hyphae. Fungal culture shows the growth of Aspergillus spp. after 05 days of incubation. **D** Section shows the absence of melanin pigment in fungus (Masson Fontana Stain × 40)

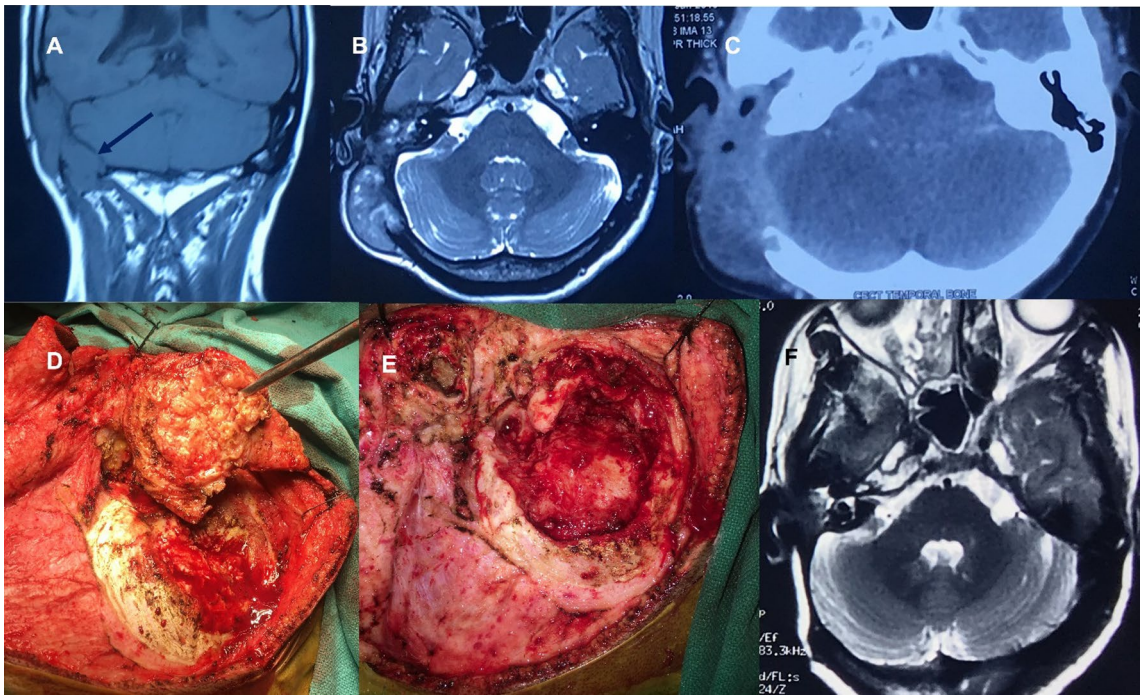

Fig. 2 Clinical images of *Aspergillus*-related CIGFD—Patient No. 1 (31-year-old female). **A** T1 non-contrast coronal MRI shows isointense extradural lesion extension into the temporal bone with cerebellar compression (Arrow). **B** T2 axial MRI shows predominant iso- to low signal mass without cerebellar edema. **C** Soft tissue contrast CT axial section demonstrates heterogeneously enhancing mass in the right temporal bone region with the erosion of the tegmen plate. **D** intraoperatively, the mass was firm and fibrous in consistency and less vascular. **E** Subtotal removal of the tumor was done with preservation of the dura. **F** Two-year follow-up T2 axial MRI shows no residual or recurrent lesion

and contrast MRI. Complaints of severe pain resolved in all nine patients (100%). The resolution of the pain took 15–35 days (mean of 22.87 days) after initiation of treatment. 6 patients (75%) showed improvement of facial palsy. Of the three patients who presented with Grade III facial palsy, two improved to Grade I; one improved to Grade II. However, one with Grade V and another patient with Grade VI facial palsy showed no improvement. 3/6 patients with IX and X cranial nerve palsy and 3/4 patients with CN XII palsy showed improvement.

Discussion

Invasive mycoses do not come up as a prominent differential while dealing with lateral skull base pathologies. Along with the fact that fungal infections of the ear and lateral skull base are infrequent, the lack of differentiating clinical and imaging features from the bacterial skull base osteomyelitis and limited options when it comes to sensitive diagnostic tests make reaching a diagnosis of a fungal etiology of lateral skull base a task to master.

A literature search, including studies up to 2020, yielded 74 individual cases of fungal temporal bone osteomyelitis; almost all were case reports. The majority of the cases were caused by *Aspergillus* spp. [6]. Needless to say, a comprehensive understanding of the fungal diseases of the temporal bone is lacking, unlike that of fungal rhinosinusitis, on which extensive discussions and classification systems have been in place [7, 8]. This case series puts forth two different Aspergillus-associated temporal bone pathologies—The *invasive skull base osteomyelitis* and *chronic invasive granulomatous disease.* While chronic invasive forms can commonly occur in both immunocompromised and immunocompetent individuals, the acute (skull base osteomyelitis) forms are more common in immunocompromised patients. But these have been reported in immunocompetent patients too [9]. In our case series, one out of the nine patients had no co-morbidity.

Aspergillus-induced chronic invasive granulomatous fungal disease of the skull base.

In anterior skull base and sinus lesions, the chronic variants, based on their histopathological findings, have been divided into granulomatous and non-granulomatous (or chronic invasive) [10]. Both are characterized by prolonged clinical course and slow disease progression. The

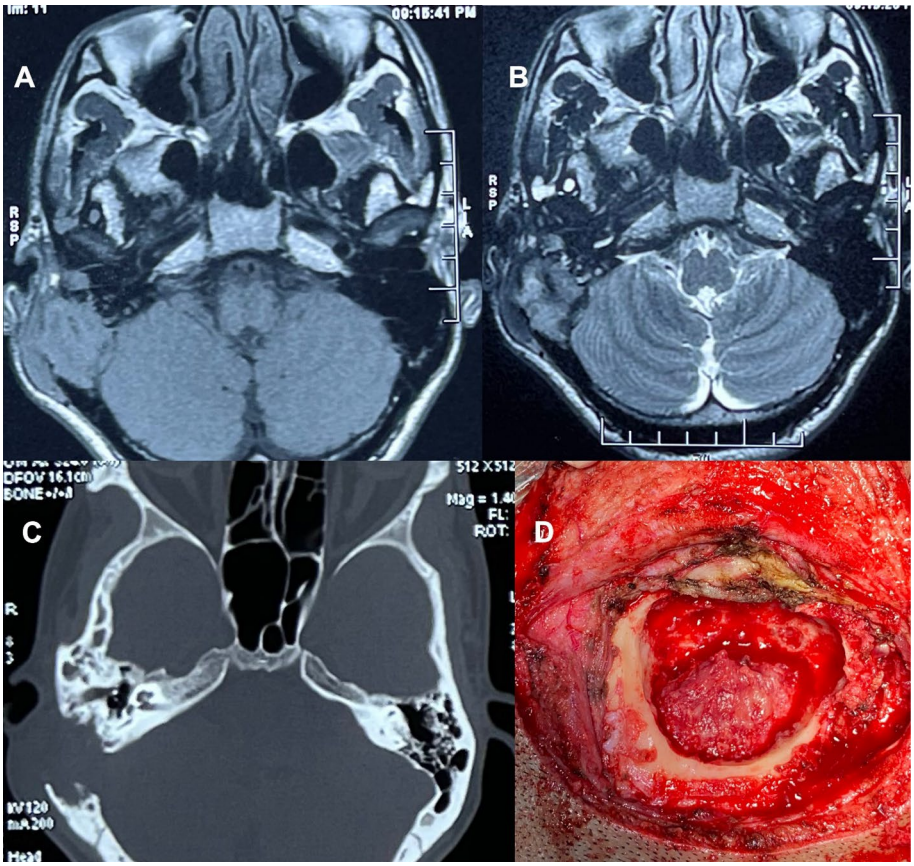

Fig. 3 Clinical images of *Aspergillus*-related CIGFD—Patient No. 2 (29-year-old male). **A** T1 non-contrast MRI shows an isointense lesion into the right mastoid with minimal cerebellar compression (Arrow). **B** T2 axial MRI shows predominant iso- to low signal mass without cerebellar edema. **C** Bone window axial CT section demonstrates destructive lesion in the right mastoid bone with the erosion of the tegmen plate. **D** Tumor cavity following subtotal removal of the tumor with preservation of dura

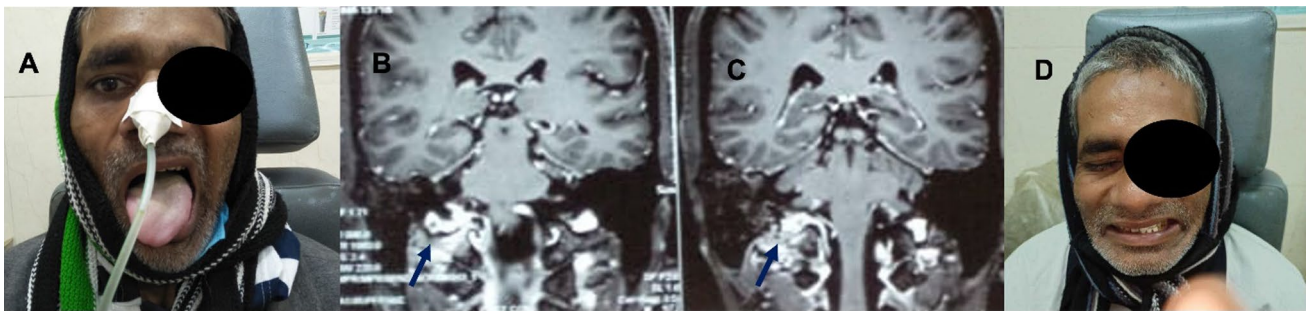

Fig. 4 Clinical images of *Aspergillus*-related skull base osteomyelitis. **A** A 45-year-old uncontrolled type 2 diabetes mellitus male patient presented 7, 9, 10, 11, and 12 cranial nerve palsy for 2 months. **B**, **C** T1 contrast coronal magnetic resonance imaging (MRI) suggestive, inflammatory lesion in the left jugular foramen (Arrow). **D** 3 months following voriconazole therapy, he had improvement in all involved cranial nerves

findings and clinical course are similar in the temporal bone disease too. Imaging characteristics of chronic invasive granulomatous forms of sino-nasal mycoses are well established; Reddy et al. described these infections as isointense on T1WI and hypointense on T2WI, which were similar in our cases despite being that of the temporal bone [11]. The essential histopathological findings that differentiate the granulomatous form from the other invasive fungal diseases are the non-caseating granulomas with fungal hyphae found within the giant cell granuloma [12]. Both patients underwent mastoid exploration with subtotal removal of the lesion. They also completed 6 months of voriconazole therapy. It is to be noted that as the patients were immunocompetent and the disease was slowly progressive, there was no pre-operative suspicion of a fungal etiology. Therefore, excision was planned for a tissue biopsy with a malignant pathology in mind.

Since the disease involved the dura, our patients were advised 6 months of voriconazole therapy, and their follow scans showed no residual or progressive lesion. The treatment for chronic invasive fungal disease is highly debatable—regarding the drug of choice and the duration of antifungal therapy. In general, surgical debulking is followed by oral voriconazole for 3–6 months or until complete remission is achieved radiologically. Since voriconazole has better CSF penetration, it is preferred as a drug for skull base invasive granulomatous fungal infections [12].

Aspergillus-induced fungal skull base osteomyelitis

Malignant otitis externa (MOE) or skull base osteomyelitis (SBO) is a potentially fatal condition with a painstakingly protracted course of treatment involving the temporal bone and skull base. With more than 98% of the cases caused by *Pseudomonas* spp., the management revolves around prolonged anti-pseudomonal antibiotics [13]. With the increasing number of immunosuppressed patients with rising use of steroids in various life-saving and transplant procedures, a growing number of diabetics around the world, immune dysregulation due to viral infections like COVID-19, along with a better clinical understanding of the condition and diagnostic modalities, fungal as a cause of SBO is increasingly becoming significant. *Aspergillus* continues to be the primary causative organism by an overwhelmingly high proportion. A scoping review of the reported case reports put *Aspergillus* spp. causing 67% of the fungal SBO reported [6].

The understanding of the causes and outcomes of the condition is still evolving. Many of the patients seem to be immunocompromised. Our series also show a similar trend. The disease progression and outcomes differ from those with immunosuppression to those without. While all our patients with diabetes mellitus presented after undergoing multiple cycles of treatments with an average duration of complaints ranging from 2 weeks to 8 months, the immunocompetent one had a very acute course of complaints developing over 2 weeks. The examination of the patient with acute course was also interesting because it revealed a lack of external auditory canal or tympanic membrane findings. The diagnosis was clinched by a blood examination which revealed a serum galactomannan level of over 3. MRI was suggestive of inflammatory changes in the left temporal skull base, and clinically the patient had cranial nerves 9 and 10 palsies. The patient, however, responded exceptionally well to Voriconazole therapy with complete resolution of symptoms over three months (Fig. 5).

On the other hand, the review by D. Macias et al. revealed that patients with diabetes showed better outcomes and lesser mortality than those without any co-morbidity [6]. The fact that immunocompromise brings in the doubt of fungal etiology earlier with the resultant initiation of antifungal therapy compared to the immunocompetent patients might be the reason for this. There was a significant delay in the symptom onset to initiation of evaluation and starting the anti-fungal therapy (2.8 and 5.2 months, respectively). This was comparable in our series, with an average of 4.6 months between initial development symptoms and anti-fungal therapy initiation. Thus, it is prudent that actions should be taken to make physicians aware of the entity of fungal/Aspergillus-induced SBO. Reducing the time to diagnose is the best way to improve the outcomes.

Diagnosis of fungal lateral skull base diseases

Diagnosis of lateral skull base pathologies is based on a multimodal approach based on history, physical examination, and laboratory and radiological findings [14]. High rates of culture-negative specimens in SBO are not uncommon, and this makes clinical suspicion and targeted evaluation very important. In the case of initially negative microbiologic studies, persistent, progressive symptoms irrespective of

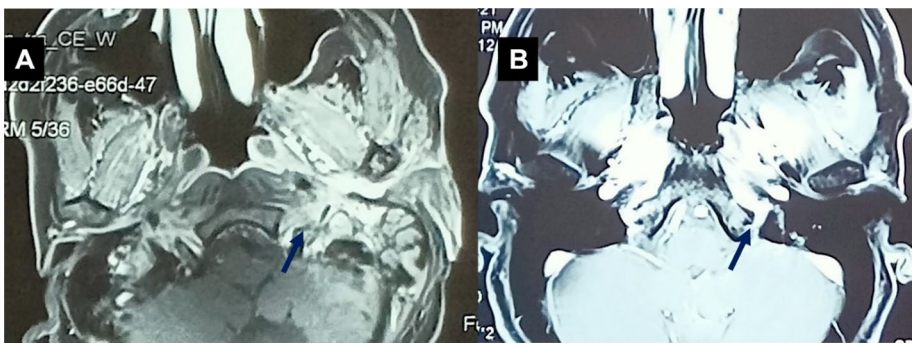

Fig. 5 Radiology of the patient with Aspergillus-related acute invasive lateral SBO. **A** 58-old-male with no co-morbidity presented with left 9, 10 cranial nerve palsy on T1 contrast axial magnetic resonance imaging (MRI) shows diffuse inflammation of the left temporal base region. **B** 3 months post voriconazole therapy, T1 contrast axial magnetic MRI shows significantly reduced inflammatory changes

the antibiotic therapy, further examination, including fungi or slow-growing pathogens, should always be performed, ideally using new molecular techniques. Therefore, non-culture-based methods, such as DNA detection by PCR or measurements of fungal biomarkers in blood or respiratory samples, are essential adjunctive tools [15]. Detection of GM antigen in plasma, serum, BAL fluid, or cerebrospinal fluid (CSF) is included in the mycological criteria that support the diagnosis of probable Invasive Aspergillosis (IA) as defined by the revised EORTC/MSG criteria [16]. For the diagnosis of invasive aspergillosis, the recommended serum galactomannan optical density (OD) is > 0.5 [17]. Galactomannan [GM] is a polysaccharide cell wall component of *Aspergillus* species released during hyphal growth in tissues in invasive infections.

Although it is neither a highly sensitive nor specific test, it could be a cheap, quick, and effective alternative to tissue biopsy, especially for a complex anatomical site like a skull base.

The use of serum galactomannan clinically guided the treatment and follow-up in our series. The clinical decisions on when to get the levels done and whether to continue antifungals or not were done on a case-to-case basis. Standardized guidelines on using the same on a wider basis need to be made.

A new assay has been developed for the point-of-care rapid diagnosis of invasive aspergillosis in which the serum was heated at 120º Celsius for 15 min without dilution. This produced a purified supernatant containing enriched mannoprotein antigen, thereby increasing the sensitivity of the test [15]. Further development in this direction is warranted, making the diagnosis of invasive fungal diseases using serum easier and straightforward.

When to suspect?

Based on the current series and the literature review, we consider it prudent to suspect a fungal lateral skull base etiology and target the investigation in this direction in the presence of the following features:

- Sudden development of lower cranial nerve palsies, especially in immunocompromised, even without any findings on ear examination.
- No improvement in symptoms in spite of culture-directed antibiotics or anti-pseudomonal coverage (in culture-negative cases).
- New onset lower cranial nerve palsies in diagnosed cases of SBO under therapy with otherwise adequate control of symptoms.
- Presence of temporal bone lesions in MRI which are isointense in T1W images and hypointense in T2W images.

How to manage?

The management of lateral skull base mycoses is primarily medical. The role of surgery is limited to providing tissue for histopathological examination and debulking of necrotic tissues in selected cases. Long-term oral voriconazole therapy can be considered for attaining good clinical control [18]. It has been shown to have better tolerability and comparable results with liposomal amphotericin, which is still the go-to drug in invasive aspergillosis (IA). Patients on long-term voriconazole treatment need regular liver enzyme monitoring—once before initiating the therapy, after 2 weeks of starting the therapy, and then once a month during the course of treatment [19]. Visual and auditory hallucinations during the initial weeks of treatment, alopecia, photosensitivity reactions, and even skin malignancies have been reported.

Other than voriconazole, newer triazoles like posaconazole and isavuconazole are also available for invasive aspergillosis. Echinocandins, including caspofungin and micafungin, can be used as salvage therapy in azole-resistant IA. Combination therapy and selective use of immunotherapeutic agents are also under various stages of development [1].

The spectrum of lateral skull base mycoses

An attempt at creating a universally accepted classification would require a bigger repository of cases with standardized methods of diagnosis and reporting. But we would like to attempt to kickstart the process with the available data from our case series and the available literature. As the lateral skull base acts as a continuum with the anterior skull base and the disease processes appear similar, we would like to apply a classification parallel to fungal rhinosinusitis and understand the spectrum of lateral skull base mycoses accordingly [7].

- *Non-invasive (Otomycosis)* The localized otomycotic debris seen usually in immunocompetent hosts with local factors leading to its formation.
- *Acute invasive (fulminant) fungal disease* usually associated with immunodeficiency and Zygomycetes spp. The authors have a couple of hitherto unreported cases of mucormycosis (COVID-19 associated) of the temporal bone presenting with sudden onset facial palsy and ear discharge. *Aspergillus* can also cause acute fulminant forms (*acute invasive lateral skull base osteomyelitis)*, as evident from a patient in this series who presented with gradually progressing lower cranial nerve palsies over 2 weeks (patient #7, Table 1). The classification of the rest of the cases is doubtful because of the delay in diagnosis; it is unclear whether the course of the disease had been acute or subacute.

Table 1 Clinical features of patients with fungal skull base osteomyelitis

S. No	Age	Presenting complaint	Co-morbidities	EAC and TM	Culture/HPE	Duration of previous treatment	Cranial nerve palsy	Serum galactomannan
1	49/M	Change in voice, RE Ache	Type IIDM	WNL	–	5 months	R 7, 9, 10, 12	0.87
2	67/M	RE Ache	Type IIDM	Granulations in posterior Canal wall	No fungal element seen on microscopy/ culture	4 months	R 7	2.80
3	38/M	RE Ache	Type IIDM	WNL	–	6 months	R 7, 9, 10, 12	3.84
4	50/M	RE Ache	Type IIDM	Discharge	Pseudomonas aeruginosa seen on culture	3 months	R 7, 9, 10, 12	2.60
5	70/M	RE Ache	Type IIDM	Discharge	No fungal elements seen	7 months	R 7, 9, 10, 12	1.00
6	66/M	LE Ache	Type IIDM	Discharge	Thin hyaline septate fungal hyphae see	3 months	L 7	1.32
7	58/M	Difficulty in swallowing	No known Co- morbidity	WNL	–	10 days	L 9, 10	3.20
8	55/M	RE Ache	Type II DM	Discharge	Pseudomonas aeruginosa seen on culture	1 Months	R 7	1.36
9	34/F	RE Ache	Type I DM	WNL	–	15 days	R 7, 9, 10	1.23

RE right ear, *LE* left ear, *R* right, *L* left, *WNL* within normal limits, *DM* diabetes mellitus

Also, there is a possibility that the disease had been bacterial (two cases had *Pseudomonas* in culture), and the fungal infection was superadded during long-term antibiotic therapy. Maybe the addition of indirect markers of fungal infection to the initial investigation panel for skull base osteomyelitis should be considered in high-risk cases.

- *Chronic invasive fungal disease Bradoo* et al. describe a case of a 65-year-old diabetic with a 1-year history of ear discharge and a 15-day history of left-sided facial palsy [4]. Histopathological examination of excised was suggestive of non-specific granulation tissue, and culture showed growth of *Aspergillus flavus.* This can be considered an example of chronic invasive fungal disease, while cases presenting similar findings but multiple cranial nerves can be considered as the *skull base osteomyelitis variant of chronic invasive fungal disease* of the temporal bone. With the current understanding, the cases (8/9 SBO cases) in our series belong to this category.
- *Chronic invasive granulomatous fungal disease* In paranasal sinuses, this is usually seen in immunocompetent, and the causative organism is commonly *Aspergillus* spp. [7]. Our case series has two cases with similar profiles. As mentioned, these are histopathologically differentiated from chronic invasive variants by "non-caseating granulomas with fungal hyphae found within the giant cell granuloma."

Conclusion

In cases of lateral skull base osteomyelitis not responding to long-term culture-directed or empirical antibiotic therapy, the possibility of fungal etiology should be considered. *Aspergillus* spp. seems to be the major fungal pathogen, and diagnosis must be based on imaging, histopathological, or indirect tests like serum galactomannan levels. While in a granulomatous variant of chronic invasive disease, surgery can be considered to obtain tissue for biopsy and debulking of fungal burden, our experience shows that long-term oral voriconazole works well to be considered the first-line therapy to obtain clinical control.

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Data availability The data is available with the authors and can be provided on request.

Declarations

Conflict of interest The authors do not have any conflict of interests to declare.

Ethical approval The Institute Ethics Committee has approved the study (IEC Code: 2022-148-IP-EXP-50).

Consent for publication Consent for publication has been obtained from the patients.

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