Fungal Skull Base Osteomyelitis Caused By Stephanoascus Ciferrii (FIRST CASE REPORT)

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Abstract: Background**:** Necrotising otitis externa is a rapidly progressing, locally invasive infection of the external auditory canal. Also known as skull base osteomyelitis, this potentially fatal condition is almost exclusively seen in immunocompromised patients, especially in elderly diabetic patients. Most of the cases are bacterial in origin, Pseudomonas being the most common causative agent. Fungal aetiology is very rare but carries a worse prognosis compared to bacterial infection, possibly due to a delay in diagnosis and due to the dose limiting adverse effects of most of the systemic anti-fungal agents. Case Presentation: We present a 67 year old diabetic patient with right fungal necrotising otitis externa, caused by Stephanoascus ciferii, a very rare but emerging fungal pathogen. The patient was successfully treated and cured with systemic voriconazole. Conclusion: This case report highlights the importance of considering the possibility of fungal aetiology in all cases of clinically suspected necrotising otitis externa, where the ear swab culture doesn't yield a proper bacterial growth. A fungal culture and sensitivity study is recommended in all such cases. In the rare event of both cultures becoming negative, voriconazole can be used as a safe empirical agent along with empirical antipseudomonal drugs. [Amjad F SEAJCRR 2018; 7(4):33-38]

Key Words: Necrotising otitis externa, Malignant otitis externa, Type 2 diabetes, Stephanoascus, Voriconazole, Fungal culture

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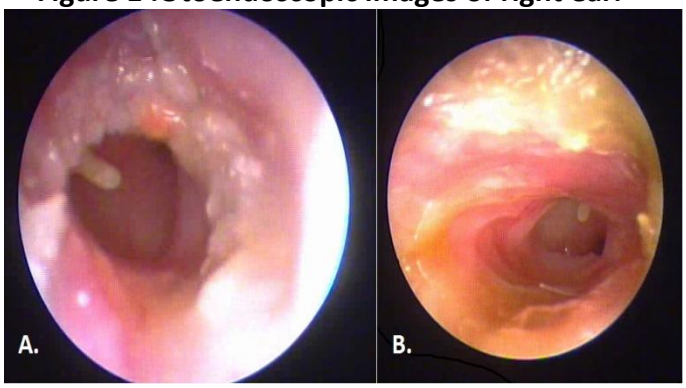
Introduction: Necrotizing otitis externa is an aggressive inflammation of the external auditory canal (EAC) characterized by severe otalgia, purulent otorrhea and granulation polyps. This potentially fatal infection typically affects immunocompromised patients and elderly diabetics[1,2]. The disease spreads via the soft tissue around the EAC to the temporal bone causing osteomyelitis, progressive cranial nerve palsies and intracranial involvement. The condition was first described by Toulmouche in 1838. Pseudomonas is the most common causative pathogen[1]. Fungal etiology is very rare and is usually found in those with AIDS, acute leukemia, long lasting nuetropenia or uncontrolled DM[3]. Being a relatively uncommon condition it is frequently overlooked by family physicians. Intensive long term antifungal therapy is the mainstay of treatment along with surgical debridement in select cases. Despite management the morbidity and mortality remains substantial due to late diagnosis, patient comorbodities and sub optimal therapy related to anti-fungal agent toxicity[4]. Non-albicans Candida spp. have been increasingly found as causative agents in human infections with important therapeutic implications. In this way, the unusual yeast species Candida ciferrii, which was first discovered in 1965 and is the anamorph of Stephanoascus ciferrii, has been described as a pathogen in superficial mycoses and very rarely in invasive disease. Here, we present a very rare case of fungal skull base osteomyelitis caused by Stephanoascus species, the first we believe to be reported to date.

Case Report : A 67-year-old gentleman with type 2 diabetes mellitus was admitted with a history of recurrent right sided ear pain and discharge of four months duration. He also had a headache and pain over the right side of the face and jaw which was aggravated by chewing and mouth opening. On examination, he had severe tragal, mastoid and temporomandibular joint tenderness on the right. The external auditory canal was tender and edematous with pale granulations and minimal discharge. There was a large central

perforation with purulent discharge in the middle ear (Figure 1A). Mouth opening was restricted by pain at the right temporomandibular joint.

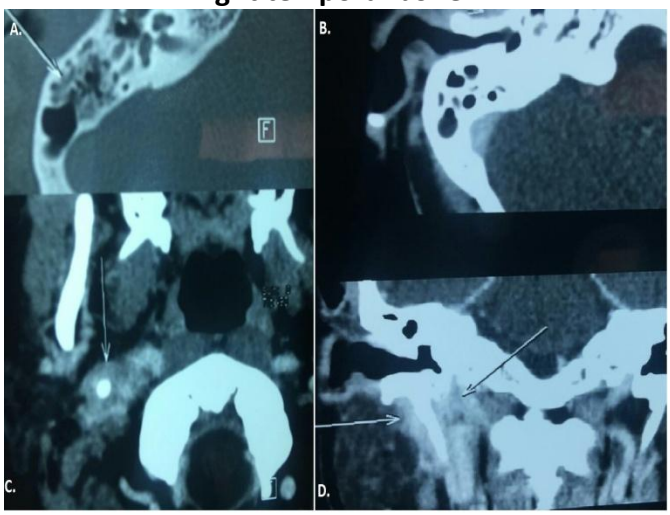
Figure 1 :Otoendoscopic images of right ear.



1A - before treatment, 1B - after resolution of infection

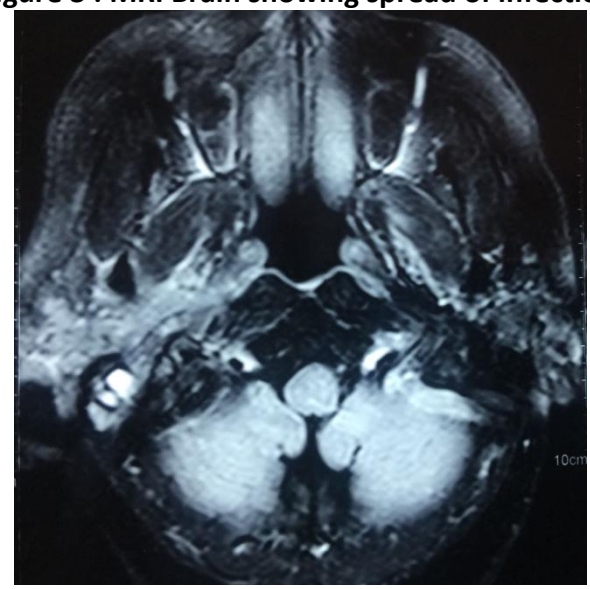
He was treated elsewhere initially with oral and topical antibiotics, which was changed to parenteral as he had no resolution of his symptoms. No bacterial growth was detected on cultures of the ear swabs and gram stain revealed candida. HRCT of the temporal bones showed infection of the right EAC and middle ear (Figure 2A), bony erosion of right TM joint (Figure 2B) and styloid process, and soft tissue infection along the right styloid and surrounding the internal carotid artery and internal jugular vein (Figure 2C & 2D). He

Figure 2: Contrast enhanced HRCT images of right temporal bone



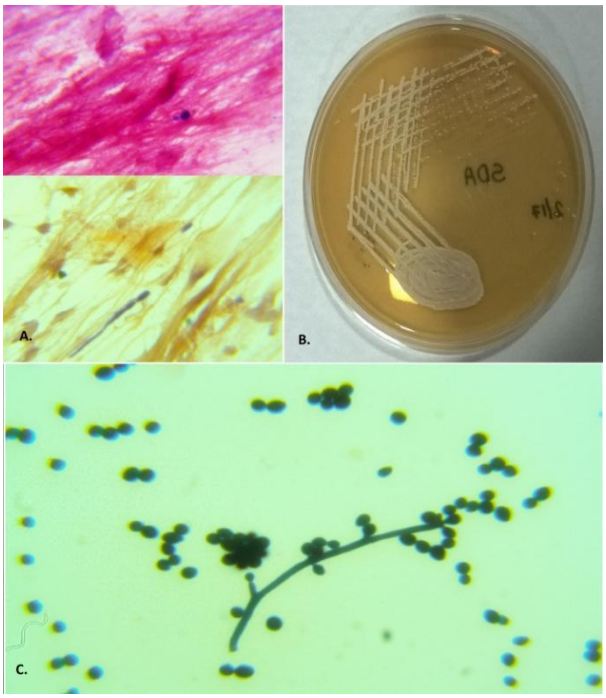
was then empirically started on anti-pseudomonal antibiotics and oral fluconazole. An MRI done after 2 weeks of IV antibiotics revealed the progression of infection to muscles around the right mastoid tip, parapharyngeal space, pterygoid muscle, parotid gland and synovial thickening of right TM joint (Figure 3). In view of the paucity of response and progression of the disease despite treatment, he was referred to us for further management.

Figure 3 : MRI Brain showing spread of infection



We repeated the routine investigations which revealed elevated total WBC counts, ESR, CRP and uncontrolled diabetes (RBS – 323mg/dL, HbA1C – 9.9). Discharge from the right EAC was sent for gram staining and culture. The patient was empirically continued on anti-pseudomonal IV antibiotics and oral fluconazole. He was switched over to insulin for DM control. There was partial resolution of the symptoms. Analgesics were gradually tapered and DM was controlled. But otorrhea and tenderness over EAC, mastoid and TM joint persisted and the inflammatory markers remained elevated. As Gram staining of the otorrhea showed only yeast-like budding cells(Figure 4A) and there was no growth on bacterial culture media, pus was sent for fungal culture. The sample was processed in duplicate containing Sabouraud dextrose agar and Sabouraud chloramphenicol agar, incubated at 37 °C and observed daily, heavy growth of yeast colonies was observed after 24 hours. The macromorphological and micromorphological characteristics of the fungal colonies were analyzed (Figure 4B, 4C).

Figure 4: The macromorphological and micromorphological characteristics of the fungal colonies



4A - Direct microscopy of clinical sample by Gram stain technique - Gram positive yeast- like budding cells of varying size arranged along the pseudo-hyphae
4B - Macroscopy of *Stephanoascus ciferrii* on Sabouraud's dextrose agar when cultured at 37 °C for 2 days. Colony of the clinical isolate was cream-colored, rough, raised and wrinkled.
4C - Microscopy of isolated *Stephanoascus ciferrii* from Sabouraud dextrose agar visualized by Gram stain technique- oval blastoconidia of varying size arranged along the pseudo-hyphae and asci.

To characterize the genus and species, and confirm the conventional mycological diagnosis, a test of characterization and identification was performed by automated Vitek 2 C system (BioMerieux ®) using Vitek identification card (ID YEAST), which was identified as *Stephanoascus ciferii*. The sensitivity testing was performed using Vitek sensitivity card (AST-YS07) and was found to be resistant to fluconazole. The minimum inhibitory concentrations (MIC) of Amphotericin B, voriconazole, caspofungin, and fluconazole were 1, 0.5, 2 and 4.5 respectively. Based on the above reports the patient was put on IV voriconazole in a dose of 200mg twice daily after a baseline liver function and ophthalmology evaluation. Gallium bone scan was considered but was not done because of non-availability. Instead, a regional FDG PET scan of the temporal bones was done for disease status evaluation as it could detect ongoing disease activity and could also be used for follow up if needed. The study reported FDG avid soft tissue thickening in the right EAC extending superiorly into the base of skull region with suspicious intracranial extension and inferiorly into the R TM joint, right carotid and parotid spaces. He was discharged 2 weeks later following complete resolution of symptoms and a fall in inflammatory markers. Voriconazole was continued orally, 200mg twice daily for 12 more weeks. He had regular follow up with monitoring of visual and liver function. The patient remains symptom-free to date (Figure 1B).

Discussion : Necrotising otitis externa, an aggressive and potentially fatal infection was described in 1959 by Meltzer[5] as a pyocyaneous osteomyelitis of the temporal bone. The condition was named Malignant Otitis Externa by Chandler who published the first case series[6]. He observed a clinically aggressive behavior along with poor treatment outcomes and high mortality rates and hence described the otitis externa as malignant. The disease originates in the EAC and progressively spreads along soft tissue and bone of the skull base and is more frequent among immunocompromised patients and elderly diabetics.

The most commonly reported causative pathogen is Pseudomonas. Other implicated bacteria are Staph. Aureus, S.epidermidis, Proteus mirabilis, Klebsiella, and diphtheroids[7]. Fungi are rarely involved in skull base osteomyelitis. Aspergillus and Candida are most commonly isolated fungi with a few reports of Sedosporium, Malassezia and Alternaria[8]. To our knowledge, this is the first case of fungal skull base osteomyelitis caused by Stephanoascus ciferii, an atypical Candida sp. This emergent pathogen is a yeast-like fungus and has been reported to have caused otitis media and superficial mycoses in humans, especially in immunocompromised hosts receiving fluconazole

as prophylactic antifungal.Drug susceptibility testing showed that it was resistant to fluconazole, flucytosine, and itraconazole, suggesting a strong tendency to become resistant[9].

Necrotising otitis externa is characterized by painful inflammation of EAC, purulent otorrhea, and granulation polyps. Otalgia is intense, nocturnal and frequently out of proportion to the clinical findings and persists after usual treatment for otitis externa. The patient may also complain of an occipital/ temporal headache and hemifacial pain. Trismus and TM joint pain are features of anterior spread. Facial and other cranial nerve involvement is common. The disease progresses through 3 stages. In the first stage, infection is limited to the EAC and adjacent soft tissues and the facial nerve may be involved at the stylomastoid foramen. In the next stage, it extends to the bone (osteitis) and multiple cranial palsies. In the final stage, the spread is extensive and involves neck spaces, large blood vessels, and intracranial structures and may even spread to the contralateral temporal bone. Death usually results from meningitis, large vessel thrombophlebitis/rupture, septicemia or pneumonia secondary to cranial nerve palsy[10]. Because of non-specific clinical presentation, the disease is often overlooked. Partially treated or unresponsive cases are particularly challenging and harbor a higher risk for complications[11]. Such cases usually present with previously negative cultures and biopsies and an exquisitely tender EAC tempting to avoid further investigations, causing further delay in diagnosis.

Fungal skull base osteomyelitis more invasive and is associated with substantial morbidity and mortality[12]. Whether the fungus is the primary pathogen or an opportunistic infection following prolonged antibiotic therapy is not known[13]. Initial cultures are frequently negative for fungus or fungal cultures are not performed unless suspected. A high index of suspicion of a fungal etiology is required when a case of skull base osteomyelitis does not respond to adequate antibiotic therapy. Whenever skull base osteomyelitis is suspected bacterial and fungal culturing of the otorrhea should be performed.

Appropriate imaging modalities can avoid delays in diagnosis. An HRCT of the temporal bones can detect cortical bone erosions and an MRI gives better details of the soft tissue extent of the disease. The most sensitive imaging is Tc99 bone scan which detects areas of osteoblastic activity. This cannot be used for follow up as uptake persists long after the infection has resolved. Gallium67 / Indium111 scans are more useful to monitoring response to treatment as it shows areas of inflammatory cell activity and the uptake returns to normal once the infection is cleared[14]. A regional FDG PET scan detects areas of ongoing disease activity and also gives better tissue details. The uptake value returns to normal with resolution of the infection and thus is useful for follow up too. However, these radionuclide scans are expensive, time-consuming and not readily available.

Long-term antifungal therapy is the mainstay of treatment. Strict control of diabetes and improving the immune status is essential in controlling the disease progression[15]. The prolonged treatment course is frequently punctuated with antifungal agent toxicities and patient comorbidities. Earlier case reports favored Amphotericin B. But low safety profile and renal toxicity often demand a decrease dosage or even interruption of treatment leading to treatment failures[16]. Later reports favor voriconazole, a broad-spectrum azole that is distributed throughout the body including soft tissues and bone[16]. Currently, it is the preferred treatment for invasive aspergillosis. The drug is well tolerated despite prolonged treatment and is available as oral and parenteral preparations. So, patients may be discharged on oral drugs once stable. Visual disturbance, deranged LFT, skin photosensitivity, and electrolyte abnormalities are the reported side effects[17]. Other drugs in use for fungal necrotizing otitis externa are fluconazole, caspofungin, and itraconazole. Hyperbaric oxygen therapy is thought to have an adjunctive role.

Surgical debridement is reserved for resistant cases and to obtain tissue for diagnosis. Some advocate prompt debridement as fungus is more invasive but others argue it might prove counterproductive as it exposes healthy bone to infection[3,10,16].There are no definite guidelines with regards to optimum therapy duration or patient selection for debridement till date.

Various protocols exist for empirical treatment of culture-negative necrotizing otitis externa to cover the most likely organisms[18]. None of these protocols include amphotericin B as its toxic nature does not justify its use as an empirical drug. Voriconazole may be considered for the purpose as it has a safer therapeutic profile.

Conclusion: Fungal necrotizing otitis externa is a rare but potentially fatal infection. Appropriate and timely investigations can avoid delay in diagnosis and prevent complications. A fungal etiology should be considered in all cases of suspected skull base osteomyelitis and we recommend that ear swabs or middle ear aspirates be sent for fungal cultures in all cases. Although there are no guidelines regarding optimum therapy duration, voriconazole is a safe and effective choice for the prolonged therapy that is required.

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