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Fungal malignant otitis externa treated with hyperbaric oxygen

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Summary
Objective: To report a case of *Aspergillus flavus* malignant otitis externa, successfully treated with antifungal agents, surgical debridement, and hyperbaric oxygen treatment.
Patient: The case was a 77-year-old man with non-insulin dependent diabetes mellitus, who presented with otalgia and purulent otorrhea. Intervention was with surgical debridement, antifungal agents, and hyperbaric oxygen treatment. The main outcome measures were radiological and histological findings.
Conclusions: A. flavus is a rare cause of malignant otitis externa. Aggressive treatment should include surgical debridement, with appropriate antifungal agents and hyperbaric oxygen therapy.

Introduction

Malignant otitis externa (MOE) is a rare, potentially fatal invasive infection of the external auditory canal. Spread to the surrounding tissues can lead to extensive osteomyelitis and cranial neuropathies. The condition is usually seen in elderly diabetics, but it is also increasingly seen in patients who are immunocompromised. Patients typically present with severe otalgia and otorrhea, which is unresponsive to topical therapy, but can also present with headache or cranial nerve neuropathies.

The majority of cases (>98%) are due to *Pseudomonas aeruginosa*[1] and the primary therapy for MOE is anti-pseudomonal antibiotics. Prior to the development of more potent and less toxic antibiotics, surgical debridement was the mainstay of treatment. Surgical management is now mainly diagnostic and constitutes an adjunctive therapy.

Fungal cases of MOE are rare, with the most common causative organism being *Aspergillus fumigatus*. In the reported cases of fungal MOE,[2,3] various management strategies were employed to treat the disease, with mixed outcomes. The following case is of MOE due to *Aspergillus flavus*, which was successfully treated with surgical debridement, aggressive antifungal agents, and hyperbaric oxygen therapy.

Case report

A 77-year-old man presented with a 5-week history of right-sided otalgia, radiating to the temporal fossa and lower jaw. He complained of aural fullness three days prior to admission. He had a past medical history of non-insulin-dependent diabetes mellitus, hypertension, and gout. On examination he had a grossly edematous right external auditory canal,

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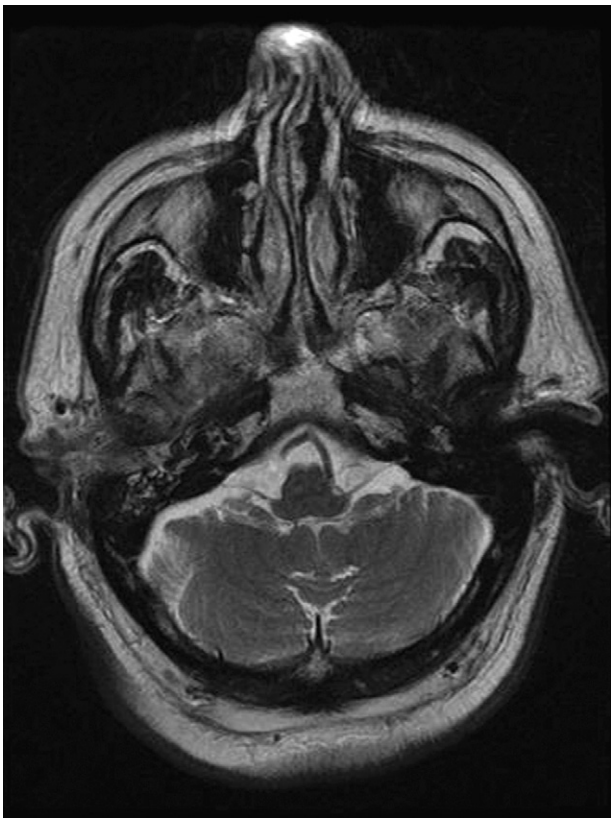

Figure 1 Magnetic resonance image showing skull base osteomyelitis.

with green discharge. The tympanic membrane was erythematous and bulging posterosuperiorly. An audiogram demonstrated bilateral, symmetrical, moderately severe high tone sensori-neural hearing loss.

The ear was swabbed and sent for microscopy, culture, and sensitivity. He was then started on empirical intravenous ticarcillin/clavulanate and oral ciprofloxacin. His symptoms worsened with increasing pain and he became more systemically unwell. Superficial swabs grew *Candida parapsilosis* and *A. flavus*.

Magnetic resonance imaging (MRI) scans showed edema and enhancement in the right external canal consistent with otitis externa, with enhancing soft tissue present in the middle ear cleft and ill defined subtemporal enhancing tissue and edema (Figure 1). There was evidence of temporal bone osteomyelitis and diffuse infra-temporal osteomyelitis, with overlying dural thickening. A gallium scan at this time also reported that there was increased activity in the right temporal bone, especially at the petrous part, consistent with our clinical impression of MOE.

The C-reactive protein (CRP) levels remained between 60 and 70 mg/l and the erythrocyte sedimentation rate (ESR) above 100 mm/h. His other blood results were within reference ranges. Clinically, he had persistent otalgia and had developed a right grade 4 House—Brackmann facial nerve palsy, with other cranial nerves intact.

Given these findings, and the worsening symptoms, a right cortical mastoidectomy was performed for debridement and collection of deep tissue biopsies. These deep tissue biopsies later isolated *A. flavus*.

He was then commenced on intravenous voriconazole and caspofungin. Minimum inhibitory concentrations (MICs) were not obtained for the isolate. Voriconazole levels were maintained at appropriate levels during this time. His blood sugar levels were managed appropriately. Hyperbaric oxygen treatment was started. This regime consisted of 30 sessions of 100% oxygen at a pressure of 2.4 atmospheres. His otalgia improved significantly and his facial nerve palsy began to resolve.

A repeat gallium scan at this time showed a reduction in gallium uptake in the temporal bone as compared to the initial study. Serial blood tests showed declining CRP levels and slowly declining ESR levels. The voriconazole was continued at 200 mg twice daily.

After an eight-week admission, the patient no longer complained of otalgia, and the right ear canal was clear of debris and his facial nerve had completely resolved. He was discharged from hospital with oral voriconazole 200 mg twice daily, with follow-up after hyperbaric treatment as an outpatient. Serial blood tests were continued, and at six weeks after discharge, the ESR and CRP levels returned to normal, and a repeat gallium scan at this time showed a further reduction in activity in the temporal bone. The voriconazole was ceased and the patient remains free of disease after 2 years.

Discussion

Fungal MOE is rare, and is most often due to *A. fumigatus*, but cases involving *A. flavus* and other species have also been reported.[2] Aspergillus are ubiquitous saprophytic moulds, commonly found on decaying material around the world. Aspergillus also produce a variety of compounds that can contribute to their pathogenicity, such as various proteases, aflatoxin, and phospholipases, and grow at a rapid rate when around 37 °C. The first line of defense against aspergillosis is the macrophages, which attach, ingest, and kill the conidia.[4] The hyphae are damaged and killed extracellularly by neutrophils, with some contribution from monocytes and macrophages.

A. flavus causes a broad spectrum of disease in humans, and this can range from hypersensitivity reactions to osteomyelitis following trauma or inoculation.[5] It can be more difficult to treat due to more resistance to antifungal agents, and has been shown to be more virulent than other *Aspergillus* species, including *A. fumigatus*. Interestingly, it has been noted that infections due to this particular fungus are more important in dry and hot climates, such as those experienced from where this case was reported. While MICs were not performed in this case, the patient made a good clinical recovery while being on a combination of voriconazole and caspofungin.

In diseased tissue, perfusion is commonly poor, resulting in low oxygen tension in these tissues. In tissues infected by Aspergillus, oxygen tension is reduced due to the fungal invasion of blood vessels, causing occlusion, thrombosis, and hypoxia.[6] Hyperbaric oxygen therapy (HBOT) greatly increases the oxygen carried in blood, so that hypoxic tissue can be returned to normal oxygen tension, or higher. A hyperoxic state also promotes the laying of collagen and angiogenesis, promoting soft tissue and bone healing.

HBOT has been studied in a variety of conditions where optimization of wound healing and microorganism killing is vital, and is used as adjunctive therapy in refractory osteomyelitis.[7] In refractory osteomyelitis, treatment failures with antibiotics and surgical debridement are often associated with systemic host and local immunocompromised factors. In MOE, treatment failure can lead to multiple cranial neuropathies and intracranial extension of the infection. Davis et al.[8] have suggested that HBOT be recommended in more advanced stages of disease, where there is skull base osteomyelitis and intracranial extension. Shupak et al.[9] suggested that HBOT be offered routinely to all cases of MOE.

The clinical picture of fungal MOE is very similar to that caused by bacteria. Often the diagnosis of fungal MOE is delayed, because treatment is usually initiated against Pseudomonas. As occurred in this case, anti-pseudomonal agents were started initially, but the lack of clinical response, and the worsening of symptoms, made the diagnosis of a bacterial cause less likely. In addition, the pathogenicity of Aspergillus may be enhanced by disruption of the normal bacterial flora in the ear, either by recent or concurrent broad-spectrum antibiotics.[10]

Conclusions

Cases of fungal MOE caused by *A. flavus* are rare, with *A. fumigatus* much more common as the fungal pathogen. The nature of *A. flavus* can make treatment difficult, as it is more virulent than *A. fumigatus* and has higher resistance to antifungal treatment. The patient reported may have been at a higher risk due to factors such as elderly age and diabetes mellitus. In treating such infections, it is important to have a high index of suspicion and to institute early and aggressive medical and surgical treatment. There may be a role for HBOT, but this may depend on the availability and accessibility of such treatments at various institutions.

Conflict of interest: No conflict of interest to declare.

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