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**Unusual Presentation of a Rare Disease: A Case Report of Fungal Necrotizing Otitis Media and Mastoiditis**

**Running title: Unexpected presentation of fungal ANOM**

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**Introduction**

Otitis media (OM) encompasses a spectrum of inflammatory conditions affecting the middle ear, including acute, recurrent, chronic otitis media, otitis media with effusion (OME), acute necrotizing otitis media (ANOM), and cholesteatoma (1). Characterized by severe middle ear infection leading to tympanic cavity necrosis, ANOM poses a significant challenge due to its severity, comparative rarity and lack of precise prevalence data (1). ANOM is frequently observed in individuals with compromised immune systems (2). While bacterial infections are the primary cause of ANOM, fungal infections are more common in the external auditory canal. Instances of invasive fungal infections originating from the mastoid and middle ear are infrequent (2). The absence of specific diagnostic criteria for ANOM, particularly regarding fungal agents, further complicates its management, highlighting the need for a well-defined protocol. This study reported a case of fungal ANOM and discussed its symptoms and management.

**Case History/examination**

A 54-year-old female, with a significant medical history for diabetes mellitus, hypertension, and end-stage renal disease (ESRD) referred to the otolaryngology clinic with intermittent right-sided ear pain for 3 months. The pain was described as dull and localized, worsening at nights, with a severity rating of 8 out of 10, accompanied by gradual deteriorating of hearing and non-pulsatile tinnitus over the past few days. The patient had no complaint of active ear discharge, facial nerve palsy, or any nasal issues.

Physical examination revealed stable vital signs and a patent external ear canal with mild edema in the right ear, along with dark-red opacification of the intact tympanic membrane, obscuring landmarks. No discharge or granulation tissues were noticed. Tuning fork examination confirmed right-sided conductive hearing loss.

**Methods**

The patient was provisionally diagnosed with possible necrotizing otitis externa (NOE) and admitted for IV antibiotics and further evaluation.

A pure tone audiogram revealed an air-bone gap (conductive hearing loss) on the right side. Tympanometry of the right ear was typing B pattern. The bone scan utilizing Technetium-99 (Tc-99m) indicated no signs of osteomyelitis in the skull base. High-resolution computed tomography (HRCT) of the temporal bone demonstrated opacification in the middle ear and mastoid air cells, without bone erosion (Figure 1). Within few days the ear condition rapidly worsened. Otoscopy on the 4th admission day, revealed total necrosis of the tympanic membrane with black discharge (Figure 2). A sample of the necrotic tissue was obtained and submitted to the medical mycology and pathology laboratories for further work-up. Direct microscopic examination of clinical specimens in 15% potassium hydroxide (KOH) showed septate, branched, hyaline hyphae along with budding cells. Moreover, the clinical specimen was inoculated on Sabouraud dextrose agar (SDA) with chloramphenicol followed by incubation at 35°C for 3-5 days. The culture results yielded *Candida* and *Aspergillus* colonies. Molecular methods revealed *C. tropicalis* and *A. flavus*, as described previously.

Consequently, liposomal amphotericin was added to the treatment regimen and the patient was scheduled for surgical debridement of the ear. Upon opening the mastoid and the antrum, it was observed that the mucosa was necrotic, the attic and mesotympanum mucosa were also abnormal and inflamed. Incus, malleolus and stapes superstructures displayed signs of necrosis, necessitating excision. Foot plate was preserved (Figure 3). The tympanic segment of the facial nerve was dehiscent. A radical mastoidectomy (canal wall down, along with closure of the eustachian tube) was also conducted.

**Outcome and follow-up**

By three weeks of IV antifungal treatment, she was free of symptoms, and discharged from the hospital on oral voriconazole to be taken for twenty more days.

On 3 months follow-up visit, the patient had no complaint of any otologic symptoms except for non-pulsatile tinnitus and hearing loss on the same ear. No sign of recurrence was detected on her examination and the mastoid cavity was completely epithelialized.

**Discussion**

Invasive aspergillosis (IA) in the middle ear is rare, with limited reported cases in the literature. Liu et al.'s comprehensive review identified only seven cases of invasive mastoiditis or acute necrotizing otitis media (ANOM) associated with aspergillosis (3). ANOM is a rapidly invasive infection, characterized by extensive middle ear necrosis, leading to the destruction of its contents and the tympanic membrane (1). In this case, initial examination only showed an opacification of the tympanic membrane. However, complete necrosis of the tympanic membrane occurred within 4 days.

ANOM particularly affects individuals with compromised immune systems, as seen in our case with concurrent diabetes mellitus and end-stage renal disease (2). While bacterial infections, notably beta-hemolytic *Streptococcus,* are common causes, there is an increasing recognition of IA as an etiological factor for ANOM. Chen et al. proposed a classification system for fungal ear infections, categorizing them based on the extent of inflammation and the presence of facial nerve palsy, aiding in tailored treatment strategies (4) (table 1).

Regarding diverse structures of the middle ear, symptoms of ANOM vary with otalgia and otorrhea being common, along with conductive hearing loss (2). Less common, facial palsy can also be observed in patients with ANOM (4).

Physical examination of the ear may suggest that the middle ear cavity may is filled with granulation tissue, with no discernible landmarks, there may be necrosis or perforation of the tympanic membrane (2). If ANOM is associated with necrotizing otitis externa, the auditory canal may be inflamed and swollen, obstructing the view of the tympanic membrane and the structures behind that. This situation may impede or even conceal the identification of ANOM.

In this case, initial presentation lacked typical signs of ANOM, highlighting diagnostic challenges. The rapid progression to tympanic membrane necrosis despite antibiotic treatment raised suspicion of fungal ANOM. Furthermore, the ear pain resolved to a good extent after 4 days of intravenous antibiotic treatment, showing the possibility of additional polymicrobial and bacterial infections. However, rapid progression to tympanic membrane necrosis despite antibiotic treatment brought about the possibility of fungal ANOM.

Treatment response was regularly monitored with erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) as depicted in Figure 4. Elevated ESR despite complete treatment and improvement of symptoms and signs could be relevant to underlying ESRD (5).

Management includes controlling underlying conditions, such as blood glucose levels, surgical removal of infected tissue, and administering antifungal medication. In cases of invasive *Aspergillus* otitis externa, many clinicians suggest a surgical biopsy for early diagnosis. Surgical debridement in the early stages is also recommended for patients who do not respond to conventional antifungal therapy (4). According to Dominik et al., if empirical treatment is unsuccessful for otogenic skull base osteomyelitis caused by invasive fungal infection, radical mastoidectomy should be performed within two weeks (3), similar to invasive fungal rhinosinusitis, in which the mainstay treatment involves radical debridement combined with antifungal therapy.

Upon admission, the immediate focus was on glycemic control. Hemodialysis was conducted three times per week. On the fifth day, after confirming the presence of IA, intravenous antifungal therapy was added to the antibiotic regimen for two weeks. Subsequently, a radical mastoidectomy was performed, and the intravenous antifungal therapy was sustained for an additional week. After consulting with an infectious disease specialist, the patient was discharged with a prescription for oral voriconazole to be taken for twenty days. This approach was successful and may serve as a reasonable strategy for similar cases.

**Conclusion**

The prognosis of invasive fungal otitis media hinges on several factors, including the patient's immune status, timely diagnosis, and aggressive treatment. Given its potential for atypical presentation, it is imperative to maintain a high index of suspicion and actively investigate for this condition, utilizing paraclinical data to aid in early diagnosis. Our case underscores the effectiveness of a multidisciplinary approach involving radical surgical debridement and full-dose antifungal therapy with amphotericin B for successful treatment of fungal otitis media caused by *C. tropicalis* and *A. flavus*. Nevertheless, further cases are warranted to refine and establish the optimal management strategy for similar presentations in the future. Continued research and collaboration within the medical community are essential for further enhancement of our understanding and management of this rare but potentially devastating condition.

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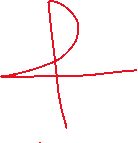
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