B-ENT, 2008, **4**, 39-43

Aspergillus mastoiditis with intact tympanic membrane in immunocompetent host

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Key-words. *Aspergillus*; masked mastoiditis

Abstract. *Aspergillus mastoiditis with intact tympanic membrane in immunocompetent host. Aspergillus* mastoiditis is a very rare condition usually observed in immunocompromised patients. Masked mastoiditis is defined as a subclinical infectious inflammatory process of the mucosal lining and bony structures of the mastoid air cells with intact tympanic membranes. To our knowledge, our report of a masked *Aspergillus* mastoiditis occurring in a 71-year-old diabetic woman is only the second case of masked mastoiditis in the literature. Aggressive medical and surgical management are necessary to avoid a fatal outcome from this invasive infection.

Introduction

In the head and neck, fungal infections most commonly involve the paranasal sinuses and the external ear. *Aspergillus* was first described in 1985 in necrotizing external otitis disease.[1] *Aspergillus* is a mold with septate hyphae of 2 to 4 µm in diameter and is identified by both gross and microscopic appearance. It is found growing on dead leaves, stored grain, compost piles and other decaying vegetation. Although human exposure to *Aspergillus* is common, infections are infrequent.

Aspergillus mastoiditis is extremely rare and is usually found in immunocompromised hosts, such as patients with acquired immunodeficiency syndrome (AIDS).[2-4] Masked mastoiditis is defined as a subclinical infectious inflammatory process of the mucosal lining and bony structures of the mastoid air cells with intact tympanic membranes.[5] Patients usually present with intracranial complications.

We present a case report of masked *Aspergillus* mastoiditis in a diabetic woman. We provide insight regarding clinical presentation, management and outcome of this very rare disease.

Case report

A 71-year-old diabetic woman presented in July 2006 to the department of Neurology with a 3-month history of resistant headache and fever. Neurological examination was normal. A computed tomographic (CT) scan showed two cerebellar abscesses of 1 and 3 cm, thrombosis of the right lateral sinus, and soft-tissue opacification of the right mastoid cells and middle ear.

Examination revealed no post-auricular fluctuance, discharge, or œdema in the external auditory canal. The tympanic membrane was intact and minimally erythematous. Tympanocentesis was performed. No fluid was obtained. A diagnosis of masked mastoiditis with intracranial complications was established. Intravenous antibiotherapy with ceftazidime, fosfomycin, and nitroimidazole was initiated and the cerebellar abscesses were neurosurgically drained. Bacteriological culture from intra-operative specimens failed to grow any organisms.

Following surgery the patient was still pyrexial and on the 10th postoperative day facial nerve function scored a 3/6 on the House-Brackmann scale. The patient was admitted to the department of Otolaryngology of Farhat Hached hospital where magnetic resonance angiography was carried out revealing two persistent cerebellar abscesses associated with lateral sinus and internal jugular vein thrombosis (Figures 1,2). A cortical mastoidectomy was performed. Intra-operative findings included lateral sinus thrombosis and subdural empyema. The empyema was evacuated and the lateral sinus was excluded. The culture of surgical specimens yielded *Aspergillus fumigatus*. Enzyme linked immunosorbent assay (ELISA) for anti-*Aspergillus* antibodies

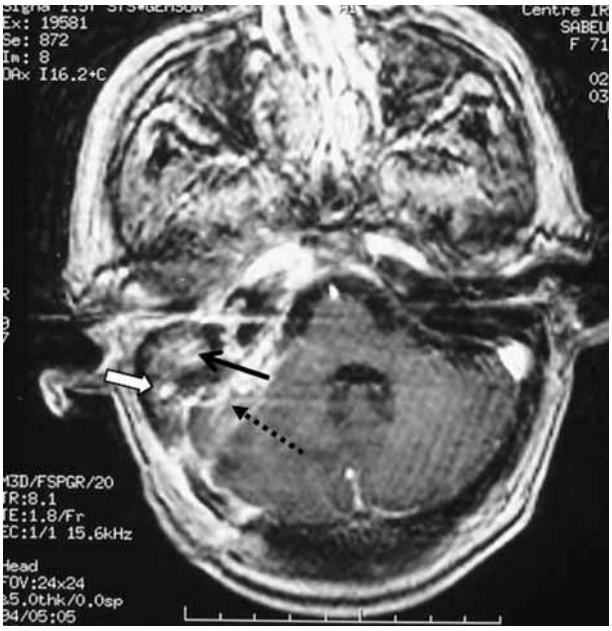

Figure 1
MRI of the temporal bone (axial view) showing an inflammatory mastoid disease (←), lateral sinus thrombosis (⇒), and subdural empyema (⇠).

Figure 2
Cerebral MRI (sagittal view) showing two cerebellar abscesses (←).

was strongly positive. Intravenous amphotericin B therapy (50 mg/day) was substituted for antibiotherapy. Anticoagulant treatment was also administered.

Facial nerve paralysis resolved in 10 days but the patient had consistent fever and became systemically unwell. Further infectious investigations (urine culture, blood cultures, chest radiograph and cardiac echography) were performed and all were negative. The patient died two weeks after the second operation from sepsis with hemodynamic failure.

Discussion

Invasive *Aspergillus* mastoiditis is a very rare disease commonly reported in patients with AIDS. The majority of AIDS patients who develop aspergillosis have neutropenia and/or are receiving corticosteroids.[4] Stanley *et al*.[6] and Slack *et al*.[7] reported cases of aspergillosis in patients with leukemia. Few cases have been reported in immunocompetent hosts. Amonoo-Kuofi *et al*.[8] described aspergillosis in a patient with systemic lupus erythematosus, and Kuruvilla *et al*.[9] reported *Aspergillus* masked mastoiditis revealed by facial nerve paralysis in a 59-year-old diabetic man.

Among the *Aspergillus* species, *Aspergillus fumigatus* is the most frequent strain producing human aspergillosis. The routes of *Aspergillus* entry to the temporal bone include nasopharyngeal spread, transtympanic, hematogenic, and meningogenic.[6] The tympanogenic route is thought to be behind infections spreading from the external canal or middle ear into the temporal bone.[7] Although our patient had no naso-sinusal symptoms, we believe the route of fungus entry was via the eustachian tube because the tympanic membrane was intact and there were no signs of meningitis or septicaemia.

The case we present is particularly interesting because the diagnosis of mastoiditis was based on intracranial complications with a normal post-auricular region and minimal tympanic membrane modifications. This defines a rare clinical form of mastoiditis called "masked mastoiditis", which developed following treatment for recent acute otitis media. Obstruction of the tympanic diaphragm by mucosal swelling, polypoid mucosa, or granulation tissue induces complete separation of the tympanic cavity from the mastoid air cells system. A low-grade local infection disease then progresses to osteitis. The intact tympanic membrane does not reflect the severity of the bone-erosion process.[5,9]

In masked mastoiditis, preoperative findings include absence of pus and presence of granulomatous

reaction,[5] also seen in mastoiditis occurring in granulomatosis diseases.[10] Intracranial complications are mainly meningitis (47%) and lateral sinus thrombosis (22%).[5] Our patient had cerebellar abscesses, subdural empyema, and thrombosis of the right lateral sinus. Cerebral aspergillosis arises most commonly from hematogenous spread from the lung, and occasionally from direct extension of paranasal sinus, middle ear, or orbital infection. Direct inoculation of *Aspergillus* spores may be also associated with intracranial surgery.[11] Although *Aspergillus* has not been shown to have neurotropic properties, nerve involvement and paresis are common findings in invasive aspergillosis.[2] Our patient developed a facial nerve paralysis which suggests *Aspergillus* is a possible mastoiditis-inducing pathogen, especially in immunocompromised patients.[2] Even in diabetic patients where cholesteatoma is not detected during mastoid exploration, we recommend sending tissue for fungal culture.

Bone scan is indicated for diagnosing mastoid osteoblastic reaction secondary to osteitis. This reaction is demonstrated by high uptake of the isotope in the involved mastoid. Although technetium 99 is the most utilized isotope,[5] indium 111 may provide more specific results.[2] CT scan and magnetic resonance imaging are also very useful, as they allow detection of frequent intracranial complications and establish a link with their otologic origin.[12]

The present case highlights the difficulty of isolating *Aspergillus* as a causal pathogen of mastoiditis. Microscopic examination of deep biopsy specimens is necessary for the diagnosis of *Aspergillus* mastoiditis. However, diagnosis of aspergillosis by histopathological section alone would be open to dispute because of the difficulty in differentiating *Aspergillus* from other fungi such

Table 1

Presentation, treatment, and outcome in previously reported cases of *Aspergillus* mastoiditis

Author	Age (years)	Underlying state	Facial nerve dysfunction	Treatment modalities	Outcome
Stanley *et al.*[6]	70	CLL	No	Amph B Flucytosine Mastoidectomy	Death at 6 weeks
Strauss *et al.*[3]	27	AIDS	Yes	Mastoidectomy Amph B Itraconazole	Death at 6 months
Yates *et al.*[4]	18	AIDS	No	Mastoidectomy Itraconazole	Death at 2 weeks
Slack *et al.*[7]	14	ALL	No	Mastoidectomy Amph B Itraconazole	Death at 6 months (due to ALL)
Chen *et al.*[2]	41	AIDS	Yes	Mastoidectomy Amph B Itraconazole	Resolved at 1 month
	36	AIDS	Yes	Mastoidectomy Amph B Itraconazole	Resolved at 6 months
	28	AIDS	Yes	Mastoidectomy	Death at 3 months
Amonoo-Kuofi *et al.*[8]	19	SLE	No	Mastoidectomy Voriconazole	Resolved at 6 weeks
Kuruvilla *et al.*[9]	59	Diabetes	Yes	Mastoidectomy Itraconazole	Resolved at 2 weeks
Present Case	71	Diabetes	Yes	Mastoidectomy Amph B	Death at 2 weeks

CLL: Chronic Lymphocytic Leukemia, ALL: Acute Lymphocytic Leukemia, SLE: Systemic Lupus Erythematosus, Amph B: Amphotericin B.

as *Penicillium* and *Cladosporium*. In our patient, tympanocentesis was negative and there was no response to initial antibacterial therapy. Only peroperative samples from subdural empyema allowed confirmation of the diagnosis after *Aspergillus* isolation. In retrospect, sending pus from cerebellar abscesses for fungal culture may have prevented the delay in diagnosis.

The management of fungal infections of the temporal bone consists of three parts: control of underlying immunologic conditions, surgical debridement of necrotic tissues, and antifungal chemotherapy.[9] The treatment depends on the extent of the disease. According to the classification proposed by Chen *et al*.,[2] type II infections (non-complicated mastoiditis) are treated by topical and systemic antifungal agents. Persistence of disease may necessitate surgical debridement with or without mastoidectomy. Treatment of type III (invasive mastoiditis with facial nerve palsy) and type IV (invasive mastoiditis, facial nerve palsy and skull base osteomyelitis) infections includes immediate and aggressive surgical debridement and systemic antifungal therapy.

Amphotericin B and itraconazole are the most effective antifungal agents against *Aspergillus*.[8] Herbrecht *et al*.[13] demonstrated in a randomized trial that initial therapy with voriconazole led to better responses and improved survival than amphotericin B in patients with invasive aspergillosis. Voriconazole was also prescribed by Amoono-kuofi *et al*.[8] in a patient with *Aspergillus* mastoiditis. The patient was treated with intravenous voriconazole at 400 mg twice daily for 1 week, followed by 200 mg administered orally twice daily for 6 weeks. The side effects and drug interaction profile of this treatment need careful evaluation. Combination therapy was reported in some cases of refractory invasive aspergillosis; one case-control study reported improved survival with a combination of voriconazole and caspofungin compared with voriconazole monotherapy.[14]

In the first reported case of masked *Aspergillus* mastoiditis,[9] treatment included canal wall down mastoidectomy and oral itraconazole at 200 mg daily. Table 1 summarizes the management and the outcome of previously reported cases of *Aspergillus* mastoiditis.

Prognosis of the disease depends on the degree of temporal bone invasion and the underlying immunologic state of the patient. Strauss *et al*.[3] concluded that lymphocyte parameters such as T4/T8 ratio, or absolute T4 cell count in AIDS patients, may be used as a guide in the selection of available therapies. Despite aggressive medical and surgical management of this disease, patient outcome is often fatal even in immunocompetent patients (Table 1).

Conclusion

Aspergillus mastoiditis is a rare but serious disease that occurs with greater frequency in immunocompromised individuals. This diagnosis should be considered when initial antimicrobial therapy directed towards more common pathogens has no effect. The clinical situation can be more difficult when intracranial complications occur first and the patient presents with masked mastoiditis. Because of the invasive nature and lethal potential of this disease, early diagnosis and aggressive management including surgical debridement and systemic antifungal therapy are necessary.

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