Malignant Otitis Externa

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Malignant (necrotizing) otitis externa (MOE) was first described as a case of progressive *Pseudomonas* osteomyelitis in the temporal bone of a patient who had diabetes nearly a half century ago [1]. Chandler [2] published the first series of patients with progressive osteomyelitis of the temporal bone and termed the condition *malignant otitis externa*. Other authors have advocated using the term *necrotizing* otitis externa to reflect the fact that the process is not neoplastic [3]. *Skull base osteomyelitis* perhaps most accurately describes the pathophysiology of the disease process and has been used to indicate infection that has spread to the skull base, beyond the external auditory canal [3]. Although perhaps less precise, *malignant otitis externa* has been used most extensively in the literature and common vernacular, and will be the term used in this article.

Before effective antibiotic regimens, MOE was frequently fatal, with mortality rates of nearly 50% [2]. Originally managed surgically, MOE is now effectively treated with antibiotics in most cases, with surgery reserved for biopsy and local debridement. Prompt identification and diagnosis of MOE and appropriate culture-directed therapy can prevent serious complications and mortality.

Epidemiology

Diabetes mellitus remains the most important associated condition. Although only 65% of subjects had diabetes in a recent review of 46 cases of malignant otitis externa [4], the prevalence of diabetes in MOE is more commonly 90% to 100% of patients [2,5–8]. Any condition causing immunosuppression, including HIV/AIDS [9,10], chemotherapy-induced aplasia, refractory anemia, chronic leukemia, lymphoma, splenectomy, neoplasia,
and renal transplantation, may predispose a patient to MOE [4,5]. As recognized in Chandler’s [2] seminal review, however, patients who have diabetes (and especially elderly patients) are particularly vulnerable to MOE because of the associated endarteritis, microangiopathy, and small vessel obliteration, which, coupled with the ability of *Pseudomonas* to invade vessel walls and cause a vasculitis with thrombosis and coagulation necrosis of surrounding tissue, underlies the pathophysiology of this disease.

Patients who have HIV-associated MOE are younger than the average patient who has diabetes. MOE should be suspected in all patients who have HIV and otitis externa that does not improve with appropriate therapy. MOE in patients who have HIV may lack typical granulation tissue along the floor of the external auditory canal (EAC) [10]. Fungal MOE is found in patients who have HIV more commonly than in those who have diabetes, particularly patients who have severe AIDS [11]. Fungal MOE often originates in the middle ear or mastoid in contrast to pseudomonal MOE. *Pseudomonas* infections in HIV occur with CD4 levels less than 100 cells/mm and *Aspergillus*-associated MOE with CD4 counts less than 50 cells/mm [9].

Although rare, MOE has been reported in children who have diabetes and other immunocompromised states, including IgG subclass deficiency [12], IgA deficiency [13], acute monocytic leukemia [14], iatrogenic neutropenia secondary to induction chemotherapy for acute lymphoblastic leukemia [15], and bone marrow transplantation [16]. Compared with adults, diabetes is not as common a comorbidity in children (21% in one review [14]) as are other immunocompromised states.

The course of MOE in children has an acute onset, with more toxic initial symptoms of fever, malaise, and leukocytosis. Although one review reported a lower incidence of facial nerve paralysis in children [14], another cited a higher incidence earlier in the course of the disease because of the less-developed mastoid process and closer proximity of the facial nerve and stylomastoid foramen to the EAC [17]. Facial paralysis has no prognostic significance to overall recovery, because both studies agree that children generally have a more favorable prognosis than adults [14,17]. Prognosis for facial nerve recovery in children is poorer, however [14]. *P aeruginosa* is also the most common causative agent in children. Complications in children include necrosis of the tympanic membrane [17], stenosis of the EAC, auricular deformity, and sensorineural and conductive hearing loss [14,17]. Most pediatric cases resolve with several weeks of intravenous antibiotics, although longer courses can be required [18]. Quinolones are generally avoided in children because of damage to weight-bearing joints in juvenile animal studies. However, ciprofloxacin has been successfully used to treat resistant MOE in a child after other intravenous therapy failed [14].

**Pathophysiology**

MOE affects immunocompromised individuals; its presentation in an otherwise healthy individual should prompt an investigation for diabetes
mellitus or other immunodeficiency. MOE originates as a soft tissue infection of the EAC. Water irrigation for cerumen disimpaction in elderly patients who have diabetes is a proposed inciting event [19]. Histologic studies of the EAC show inflammation of the epidermis with acute and chronic inflammatory reaction in the dermis [20]. Patients who have diabetes show poor chemotaxis and phagocytosis of polymorphonuclear leukocytes, monocytes, and macrophages, leading to susceptibility to *P. aeruginosa* infection [21,22]. Another contributing factor may be the higher pH of cerumen in individuals who have diabetes [23].

Infection from the EAC spreads to the skull base through the fissures of Santorini, small perforations in the cartilaginous portion of the EAC found along the floor of the canal. Once out of the canal, infection spreads medially to the tympanomastoid suture, and along venous canals and fascial planes. The compact bone of the skull base becomes replaced with granulation tissue, leading to bone destruction. Progressive spread of infection to skull base foramina causes cranial neuropathies. The most commonly involved nerve is the facial nerve because of the proximity of the stylomastoid foramen to the EAC. Nerves of the jugular foramen are the next most commonly affected. As disease spreads more medially, petrous apex involvement can affect the abducens and trigeminal nerves and, more medially, the optic nerve [24]. Spread of infection to the sigmoid sinus can lead to septic thrombosis of the sigmoid sinus and internal jugular vein; meningitis and cerebral abscess may also complicate MOE [3,25]. Skull base osteomyelitis can also spread to the contralateral side and include the cervical spine [26]. Finally, extracranial spread of infection may involve the infratemporal fossa, parotid, and neck, leading to involvement of surrounding structures and abscess formation. The otic capsule is typically spared and middle ear involvement is usually a late finding [2,3].

**Microbiology**

In most cases, the causative agent of MOE is *Pseudomonas aeruginosa*, which is a gram-negative obligate aerobe not normally found in the EAC. This organism will colonize the EAC in a moist environment or after trauma and is only a pathogen in the absence of effective host defenses. It also commonly causes benign acute otitis externa (swimmer’s ear). Conditions leading to more invasive MOE must also involve impaired host immunity to allow the organism to spread out of the external canal. More virulent *Pseudomonas* species contain a mucoid surface layer that protects the bacterium from phagocytosis. They also produce lytic enzymes, including endotoxin, collagenase, and elastase, causing a necrotizing vasculitis and endarteritis that enable invasion of surrounding tissue. Other bacteria, including *Staphylococcus aureus* [27], *S. epidermidis* [28], *Proteus mirabilis* [29], *Klebsiella oxytoca* [30], and *P. cepacia* [31], have also been reported to cause MOE, although these organisms may have been colonizers and not true pathogens.
Fungal pathogens can also cause MOE, particularly in immunocompromised patients who are not diabetic, including those who have HIV/AIDS [25]. The most common fungal organism is *Aspergillus fumigatus* [32,33], although other species have been isolated, including *A flavus* [34,35], *A niger* (in a patient who was immunocompetent [36] and one who was diabetic [37]), and *Scedosporium apiospermum* (in a patient who had end-stage AIDS [11]). The possibility of fungal MOE must be considered if a patient who has classic signs and symptoms of MOE is unresponsive to appropriate antimicrobial therapy and cultures have been negative. Fungal MOE should also be considered and cultures retaken in patients who do well initially on antimicrobial therapy but experience recrudescence [34]. Several studies point out the clinical differences between bacterial and fungal MOE (Table 1).

Finally, the diagnosis and treatment of MOE in the absence of an identifiable pathogen (culture-negative specimen) has been described. These studies diagnosed MOE based on clinical history, signs and symptoms, biopsy to rule out malignancy, markedly elevated erythrocyte sedimentation rate (ESR), and imaging studies, such as CT and radionuclide (gallium and technetium bone) scanning [8,38]. Previous treatment with oral or topical antibiotics before evaluation and wound culture may be responsible for this scenario, because many patients had already experienced failed response to a short course of oral ciprofloxacin and various topical antibiotic preparations before undergoing otolaryngologic evaluation. Treatment included intravenous ceftazidime (aztreonam for penicillin allergic patients), high-dose oral ciprofloxacin (750 mg twice daily), and topical aminoglycoside–steroid drops [8].

**Clinical presentation**

Typical patients who have MOE are elderly individuals who have diabetes and severe, unremitting otalgia, aural fullness, otorrhea, and hearing loss. Otalgia in these patients may be worse at night and more severe than what is usually associated with otitis externa. Hearing loss is conductive in nature. Headache, temporomandibular joint pain, and decreased oral intake secondary to trismus may also be present. Patients may provide a history of minor ear canal trauma associated with irrigation or cleaning. Many patients will have already taken short courses of oral antibiotics or been prescribed topical antibiotic drops. This antecedent history of antimicrobial therapy should not deter clinicians from pursuing and diagnosing MOE (and ruling out malignancy).

On examination, purulent otorrhea with a swollen, tender external auditory canal are hallmarks. Skin of the concha may be erythematous and tender. Granulation tissue or exposed bone is frequently seen on the floor of the canal at the bony–cartilaginous junction. Usually the tympanic membrane and middle ear appear healthy and uninvolved if not obstructed by granulation tissue or polyp in the canal. Periaural lymphadenopathy may
Table 1
Clinical and microscopic differences between bacterial and fungal malignant otitis externa

<table>
<thead>
<tr>
<th>Etiologic agent</th>
<th>Age</th>
<th>Diabetes</th>
<th>Immunosuppression</th>
<th>Granulation tissue</th>
<th>Middle ear/mastoid involvement</th>
<th>Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteria (Pseudomonas aeruginosa)</td>
<td>Older</td>
<td>Common</td>
<td>Common</td>
<td>+</td>
<td>−</td>
<td>Gram-negative rod</td>
</tr>
<tr>
<td>Fungus (Aspergillus spp)</td>
<td>Younger</td>
<td>Less common</td>
<td>More common, especially cellular immunity, AIDS</td>
<td>−</td>
<td>+</td>
<td>Branching septated hyphae; calcium oxalate crystals [36]</td>
</tr>
</tbody>
</table>

*Abbreviations: +, present; −, absent.

*Data from Refs. [34–36].
also be present. Associated cranial neuropathies are caused by spread of infection through the skull base. Involvement of the stylomastoid foramen will lead to facial paralysis in 25% of patients; less frequently, involvement of the jugular foramen leads to deficits in cranial nerves IX, X, and XI [7,12]. Fever and leukocytosis are frequently absent. Dural sinus thrombosis, meningitis, and cerebral abscess may also complicate MOE and are late findings that portend a grave prognosis. The diagnosis of MOE should be considered in all immunocompromised patients, especially those who have diabetes, who have external otitis and severe otalgia.

Diagnosis

The diagnosis of MOE relies on specific elements of the history and physical examination and laboratory and imaging studies. Findings of pain disproportionate to the examination, otorrhea, and granulation tissue along the floor of the ear canal at the bony–cartilaginous junction are usually the first nonspecific signs and symptoms of MOE. Differential diagnosis includes carcinoma of the ear canal, granulomatous diseases, Paget’s disease, nasopharyngeal malignances, clival lesions, and fibrous dysplasia [25]. Carcinoma of the ear canal has similar clinical and radiologic findings, and biopsy is absolutely necessary to rule out this disease. Additionally, repeat biopsy and cultures are warranted to rule out an occult malignancy if inflammatory disease persists despite appropriate antibiotic therapy. Fever and leukocytosis are typically absent in adults who have MOE. ESR is always elevated and has been advocated as a nonspecific inflammatory marker for diagnosis and resolution of disease [39].

Even if patients have used antibiotic drops, cultures should be taken for aerobic, anaerobic, and fungal organisms and for bacterial sensitivity. Tissue biopsies should be sent to pathology to rule out malignancy and to microbiology for culture. Silver stain on histologic sections may identify fungal pathogens. Repeat cultures are necessary if the first set of cultures is negative, but withholding therapy until cultures are positive is not recommended.

No imaging modality provides adequate anatomic and physiologic detail sufficient to diagnose and follow MOE. CT is sensitive to bone erosion and decreased skull base density, a later finding in MOE (Fig. 1) [40,41]. CT scanning is also sensitive in diagnosing abscess formation and involvement of the mastoid, temporomandibular joint, infratemporal fossa, nasopharynx, petrous apex, and carotid canal. Demineralization of the skull base of 30% or greater is identifiable on CT scan, but because these changes persist despite resolution of disease, CT is therefore a poor choice for measuring treatment response. CT is also inadequate for showing intracranial extension and bone marrow involvement.

MRI better shows changes in soft tissue, particularly dural enhancement and involvement of medullary bone spaces [41]. The persistence of these radiographic changes despite resolution of disease also makes MRI
a poor study for determining disease resolution. Involvement of the retrocondylar fat pad on MRI has been proposed as an early diagnostic finding in patients being evaluated for MOE [42], but MRI is generally not recommended as a first-line diagnostic imaging modality (given its lower sensitivity for imaging bone erosion compared with CT).

Nuclear imaging has been a mainstay in the diagnosis and follow-up evaluation of patients who have MOE. Technetium Tc 99m methylene diphosphonate (MDP) scintigraphy (bone scan) is positive in almost 100% of MOE cases (Fig. 2). Technetium Tc 99m MDP radiotracer concentrates in areas with osteoblastic activity, as found in infection, trauma, and neoplasm. Given its high sensitivity, technetium Tc 99m MDP imaging allows earlier diagnosis of osteomyelitis than CT [43]. Sensitivity for MOE can be improved through identifying increased uptake between 4 and 24 hours postinjection [44]. However, technetium Tc 99m MDP scans are not specific for infection; they will also be positive in malignancy, hence the need to rule out malignancy with tissue biopsy. Technetium Tc 99m MDP bone scans remain positive indefinitely and are therefore not useful as markers of response to therapy or disease resolution.

Gallium Ga 67 citrate concentrates in areas of active inflammation through attaching to lactoferrin, which is present in large quantities in leukocytes, and through binding to transferrin and bacteria directly [45]. Gallium scans will be positive for soft tissue and bone infections (Fig. 3). Gallium uptake returns to normal after the infection has cleared, and several studies have suggested repeating gallium studies every 4 weeks to assess treatment response, and as a reliable test to stop treatment if negative [25,46]. Gallium scans have also proven useful in detecting recurrent disease.
Both gallium and technetium Tc 99m MDP scans show poor anatomic resolution but are complementary in the diagnosis of MOE (Table 2).

**Management**

Successful management of MOE frequently requires collaboration with an endocrinologist, neurologist, radiologist, and infectious disease specialist.

Fig. 2. Anterior and posterior views of technetium Tc 99m MDP bone scan of patient from Fig. 1 showing increased uptake in the left mastoid.

Fig. 3. Gallium scan of patient from Fig. 1 indicating increased inflammatory activity in the left mastoid region on posterior (A) and left lateral (B) views.
Important principles of treatment include aggressive control of diabetes, reversal of acidosis, and improvement of immunocompetency, where possible. Although surgical intervention is no longer standard care for MOE, therapy does require biopsy and culture, and may require local debridement of granulation tissue and bony sequestration or drainage of associated abscess. Long-term antibiotic therapy is the mainstay of MOE treatment. Culture-directed therapy should always be the goal of treatment, and should be continued for at least 6 to 8 weeks. Previously, antipseudomonal penicillins and aminoglycosides were commonly used. This effective combination required parenteral administration and monitoring for ototoxicity and nephrotoxicity, especially in patients who had diabetes prone to chronic renal insufficiency.

Long-term monotherapy with oral ciprofloxacin (750 mg twice daily) has been proposed as the preferred initial antibiotic regimen [6]. Fluoroquinolones are active against \emph{P. aeruginosa}, penetrate bone well, have excellent oral bioavailability, and a less significant side effect profile compared with alternatives. Addition of rifampin, which does not affect the pharmacokinetics or bactericidal activity of ciprofloxacin, has also been suggested in MOE [39]. Newer-generation oral fluoroquinolone antibiotics other than ciprofloxacin may also be considered, but none has been reported in MOE.

Increasing incidence of pseudomonal resistance to ciprofloxacin has more recently been reported [5]. Resistance is related to widespread use of quinolones in the treatment of upper respiratory infections, topical preparations for otitis media and externa, and inadequate treatment courses in MOE. Be renholz and colleagues [5] found 33% \emph{P. aeruginosa} in MOE were resistant to ciprofloxacin. At the University of Virginia, resistance to \emph{P. aeruginosa} runs 20% in the outpatient setting. Avoidance of topical quinolones in non-invasive external ear infections, in favor of acidifying agents such as boric and acetic acid, has been recommended [5,19]. Use of topical antibiotics in MOE is controversial because these preparations only change bacterial flora of the EAC, making culture more difficult and introducing a potential source of antibiotic resistance without adding significant benefit [19,25].
Third-generation cephalosporins with antipseudomonal activity, such as ceftazidime, provide an alternative to ciprofloxacin in the treatment of MOE [5,47,48]. Ceftazidime requires parenteral administration, with resultant increased treatment cost and inconvenience to patients. Use of a concurrent aminoglycoside has also been recommended in resistant and complicated cases [49,50].

Amphotericin B is the most commonly used antifungal agent for fungal MOE [32–35], but alternatives have been sought given its toxicity. Liposomal amphotericin B is a lipid formulation of the drug with lower toxicity and equal efficacy. Oral itraconazole has also been used after a successful short course of amphotericin B [11].

Recurrence rates of 15% to 20% have been reported for MOE [26]. In this study, three elderly patients who had diabetes experienced recurrence of inadequately treated MOE, resulting in death in two patients and significant morbidity in the third. In all cases, inadequate length of treatment with resolution of symptoms preceded recurrence. Despite relief of symptoms, prolonged treatment of 6 to 8 weeks is recommended. Therapy can be discontinued once the ESR and gallium scans have normalized. Close follow-up is still necessary, because recurrence of MOE up to a year has been reported.

The role of hyperbaric oxygen (HBO) in managing MOE is not well established. HBO increases the partial pressure of oxygen, improving hypoxia and allowing greater oxidative killing of bacteria. Some authors have advocated its use in MOE for refractory skull base osteomyelitis [18,26,51,52] and intracranial involvement [53]. HBO requires daily treatments for several weeks and side effects include oxygen toxicity, barotrauma, and tympanic membrane perforation. A thorough review of the Cochrane Database, Medline, and Embase found no randomized controlled trials of HBO in MOE and concluded that no clear evidence exists to show the efficacy of HBO compared with antibiotic or surgical treatment [54].

Mortality from MOE has decreased from greater than 50% [2] to 0% to 15% [51]. Facial palsy has been suggested to signify poor prognosis, indicating the need for a longer course of treatment before recovery [4]. Poor prognostic factors include Aspergillus infection [4] and MRI findings of middle cranial fossa and foramen magnum dural enhancement [42]. In a recent series of 23 patients, cranial nerve involvement was not associated with poorer outcome, as was reported previously [7]. In this study, lower cranial nerve dysfunction exhibited good recovery, whereas facial nerve function improved but some dysfunction persisted despite adequate treatment. These results indicate that with current therapy, cranial nerve involvement does not preclude cure, although patients may have incomplete recovery of facial nerve function.

**Summary**

MOE should be suspected in immunocompromised patients (especially those who have diabetes) who have severe otalgia, purulent otorrhea, and
granulation tissue or exposed bone in the external auditory canal. Prompt diagnosis with nuclear and CT imaging, biopsy to rule out malignancy, and culture (aerobic, anaerobic, and fungal) is essential. Antimicrobial therapy, generally starting with a high-dose oral quinolone, may avert complications of MOE, including cranial neuropathies and even death. Resolution of symptoms, especially pain, along with follow-up gallium scanning directs length of therapy, which should continue for at least 6 weeks.

Acknowledgments

The authors wish to thank Brian Williamson, MD, for assistance with the radiologic images and text.

References


