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Malignant otitis externa in the antibiotic resistance era: key to successful treatment

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Abstract. *Malignant otitis externa in the antibiotic resistance era: key to successful treatment. Objective*: Malignant otitis externa (MOE) is a rare aggressive, necrotizing infection of the external auditory canal and the temporal bone. MOE may have a poor prognosis when it is not treated promptly and adequately. It is most commonly reported in males, older individuals, patients with diabetes, or patients that are immunocompromised. *Pseudomonas aeruginosa* is the main pathogenic agent involved. This study aimed to evaluate a clinical series of patients with MOE and discuss the current literature on the topic.
Methodology: This retrospective study included 8 patients with MOE that were evaluated and treated, medically and/or surgically, at the University Hospital of Ferrara between January 2012 and December 2016. We retrieved data from medical records on the clinical history, imaging, and treatment.
Results: In all cases, a microbiological examination disclosed the presence of *P. aeruginosa*. The infection was eventually controlled in all cases, after a median of 6 months of therapy. All patients were followed-up for an average of 12 months after infection resolution.
Conclusion: Currently, no specific guidelines for MOE treatment are available in the literature. Based on our findings, we proposed a diagnostic and therapeutic flow-chart for managing this infection.

Introduction

Malignant otitis externa (MOE) is a rare aggressive, necrotizing infection of the external auditory canal and the temporal bone; it most commonly affects older patients, patients with diabetes, and/or patients that are immunocompromised (e.g., due to AIDS, chemotherapy, rheumatologic conditions, or autoimmunity).[1-10] *Pseudomonas aeruginosa* is the main agent involved in MOE pathogenesis, although other bacteria may be involved, such as *Staphylococcus aureus*, *Klebsiella* spp., and *Aspergillus* spp.[110] MOE typically arises as an infection in the tissues of the ear canal at the bony-cartilaginous junction. It spreads quickly to the surrounding tissues, then towards the temporal bone and skull base. The most frequent symptom of MOE is intense otalgia, which is often associated with temporal or occipital headache. Disease manifestations include painful inflammation of the external ear canal, associated with purulent otorrhea and granulated polyps. MOE is histologically identified by inflammatory cell infiltration and hyperplasia of the squamous epithelium.[1-10] Three clinical stages have been described. The first stage is an infection of the external auditory canal and adjacent soft tissues with severe pain, with or without facial nerve palsy. The second stage is characterized by infection extension, with osteitis of the skull base and temporal bone, or multiple cranial nerve neuropathies. In the third stage, the infection reaches the intracranial structures, neck spaces, and large blood vessels.[1-10] Achieving an early diagnosis is often difficult, because the clinical findings in the early stages of MOE are similar to those of classical external otitis. Diagnostic delays and the consequent lack of prompt, adequate treatment lead to successive evolution of the pathology.[1-10]

This study aimed to evaluate the management of 8 cases of MOE, and to review the literature, focusing particularly on the staging and management of this disease.

Patients and methods

This retrospective study included 8 patients with MOE. All patients were evaluated and treated at the ENT & Audiology Department and at the Infectious Diseases Department of the University Hospital of Ferrara, from January 2012 to December 2016. For each patient, we collected all data concerning the clinical history, clinical examinations, laboratory data, microbiological findings, imaging, and treatment.

Diagnosis of MOE was defined, based on (*i*) a clinical history of recurrent otitis externa or otitis resistant to therapies in patients with diabetes; (*ii*) isolation of *P. aeruginosa* in the microbiological examination of the aural discharge; and (*iii*) radiological signs of temporal bone involvement. All patients were treated for a median of 6 months. Therefore, follow-up was conducted in the subsequent months.

This study was compliant with the Helsinki Declaration (2008). Informed consent was not required, due to the retrospective and observational design of this study, which did not affect patient care in any way. Nevertheless, all subjects were informed about the research project during the visits, and they all consented to participate in the study.

Results

Our series of patients with MOE were mostly male (7/8). The average age at diagnosis was 75.1 (±5) years. Among the observed comorbidities, all patients had inadequately managed diabetes mellitus (HbA1c >8%). In all cases, the clinical history was characterized by a recurrent or persistent external otitis that had lasted at least one month, despite numerous attempted treatments. Patients were mainly treated with oral amoxicillin, associated with aural irrigation with antiseptic agents or topical antibiotics, such as aminoglycosides or fluoroquinolones. The main clinical features of the patients are shown in Table 1.

All patients complained of ear pain and purulent discharge at diagnosis. One patient also reported other symptoms, including nocturnal nuchal headache and progressive dysphagia.

The laboratory tests showed that 4/8 cases had ESR (Erythrocyte Sedimentation Rate) >140 mm and CRP (C-Reactive Protein) >110 mg/l.

Table 1
Clinical features of patients with malignant otitis externa

CASE	GENDER	AGE	COMORBIDITY
1	M	96	TYPE 2 DM
2	M	64	TYPE 2 DM + chronic renal failure
3	M	69	TYPE 2 DM
4	F	82	TYPE 2 DM + COPD + ischemic cardiopathy + bed-blocked + cerebrovascular disease
5	M	85	TYPE 2 DM + arterial hypertension + bearer of pace maker + chronic renal failure + previous ischemic ictus
6	M	74	TYPE 2 DM
7	M	65	TYPE 2 DM + arterial hypertension
8	M	66	TYPE 2 DM + arterial hypertension + previous ischemic ictus

DM: Diabetes Mellitus; COPD: chronic obstructive pulmonary disease.

The micro-otoscopic examinations disclosed, in 5 cases, purulent otorrhea, with granulated tissue and cartilaginous segregation of the ear canal; in 3 cases, the presence of a polypoid formation. In all cases, the tympanic membrane was thickened and hyperemic. One case presented a concomitant multiple cranial nerve palsy (VII, IX, XI, XII).
All the microbiological examinations disclosed the presence of *P. aeruginosa*.

All patients underwent a temporal bone CT scan: all cases presented mastoid involvement and a thickening of the external auditory canal (EAC). Some bone erosion of the EAC was evidenced in 6 patients; mandibular condyle erosion was observed in 2 subjects; and skull base osteomyelitis with

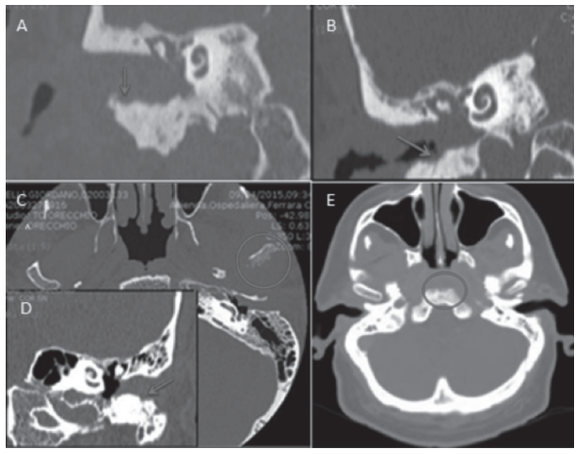

Figure 1
Coronal (A,B,D) and axial (C,E) CT scans of cranial bone in a patient with malignant otitis externa. Cortical bone erosion (*red arrows*) is apparent in the left mastoid and the clivus.

Table 2
Therapeutic procedures performed in patients with malignant otitis externa

CASE	CIPROFLOXACIN	CEFDITOREN	CEFTRIAXONE + CLINDAMYCIN	MEROPENEM	CEFTAZIDIME	SURGERY
P.M.	X	X	-	-	-	-
M.G.	-	-	X	X	-	-
C.P.	X	-	X	-	-	Canal Plasty, Mastoidectomy-tympanoplasty
C.C.	X	-	-	X	-	-
F.M.	X	X	-	-	-	-
C.F.	X	X	-	-	-	-
P.G. dx	X	-	X	-	-	Canal plasty
P.G. sx	X	-	-	-	X	Myringotomy with tube insertion

Table 3
Therapeutic strategies adopted for 8 patients with malignant otitis externa

FIRST LINE TREATMENT	SECOND LINE TREATMENT	INTRAVENOUS THIRD LINE TREATMENT	SURGICAL TREATMENT
• Control of Diabetes Mellitus • Periodic debridement of necrotic tissue in micro-otoscopy and ear lavages with antiseptic solutions • Oral and topical high-dose **fluoroquinolone** (ciprofloxacin 500mg or 750mg every 12h for at least 2 weeks)	• Oral **third generation Cephalosporin** (cefditoren 400mg every 12h for at least 2 weeks)	• **Meropenem** 2g every 8h • **Third generation Cephalosporin** (associated with other category of antibiotics) Ceftriaxone 2g every 24h + Clindamycin 600 or 900mg every 6h • Ceftazidime 1g every 6h + Ciprofloxacin 400mg every 12h	To perform biopsies on deep tissues and to exclude overlapping - neoplasms - invasive fungal infection

clivus erosion was observed in 2 cases. In one case, cortical erosion of the mastoid bone was also observed (Figure 1). MRI scans were performed only in selected cases.

Therapeutic procedures are summarized in Table 2. In most cases, a combination of antibiotics was administered. The goals of the therapeutic strategies (Table 3) were: (*i*) to control diabetes mellitus adequately; (*ii*) to debride necrotic tissue periodically, with micro-otoscopic guidance and with local antiseptic solutions; and (*iii*) to provide systemic and topical antimicrobial therapies, with high-dose fluoroquinolone (ciprofloxacin 500 or 750 mg every 12 h) for at least 2 weeks. Patients also received systemic administration of a high-dose, third-generation cephalosporin (i.e., cefditoren 400 mg every 12 h) for at least 15 days, usually in combination with ciprofloxacin. Three patients that were resistant to therapy were hospitalized and given intravenous carbapenems or third-generation cephalosporins.

A surgical approach was required for two patients that did not respond to medical treatment. One case, which was complicated with skull base osteomyelitis that involved the VII, IX, and X cranial nerves, exhibited an overlapping, invasive fungal infection (*Aspergillus fumigatus*). Intravenous voriconazole was administered (400 mg every 12 h for the first day, followed by 200 mg/day), prior to hospitalization in the Infectious Diseases Department. That patient experienced symptom remission after 1 month of treatment (although a grade III House-Brackmann facial nerve paralysis persisted). The other patient also received trans-tympanic drainage.

In all cases, the infection was controlled after a median of 6 months of therapy. All patients were followed-up for an average of 12 months after resolution of the infection.

Discussion and Conclusion

MOE is thought to appear most commonly in individuals with diabetes mellitus; however, it can also occur in individuals with HIV infections, in those treated with immunosuppressive therapies, or in those affected by oncohematologic diseases.[1] Its frequency has increased over time, and its prevalence has doubled in the last decade, probably due to the greater prevalence of (*i*) diabetes mellitus, and (*ii*) a longer life span, which has resulted in an older population.[2] MOE mortality has not been correlated with age, gender, the degree of glucose tolerance, the duration of diabetes, the type of microorganism, comorbidities, or the involvement of a single cranial nerve. MOE mortality has mainly been correlated with the duration of hospitalization, surgical therapy (when performed), skull base involvement, the presence of intracranial extension, and multiple cranial nerve palsy.[3,4] Adequate, prompt treatment has always been advocated. Levenson proposed clinical criteria for diagnosing MOE, including: refractory otitis externa, severe nocturnal otalgia, purulent otorrhea, the presence of granulated tissue in the external auditory canal, growth of *Pseudomonas*, and the presence of diabetes mellitus or an immunocompromised state.[5] In some cases, facial nerve palsy might also occur.[6,7] *P. aeruginosa* is the most commonly isolated microorganism, as found in the present study;[8] however, in some cases, other microorganisms have been identified.[8] Invasive mycotic involvement should be suspected when the infection is resistant to antipseudomonal treatment, when the culture examinations are negative, and when patients carry HIV.[9] In these

cases, surgical debridement of necrotic tissue in the external auditory canal should be followed by a deep tissue biopsy. This biopsy is essential for histopathological confirmation of an invasive fungal infection.[6,10] *Aspergillus spp.* is the most commonly involved mycete, in these cases.[6,10]

A temporal bone CT scan is always necessary to evaluate bone erosion of the ear canal, as indicated previously by several authors.[6,11,12] A conventional MRI allows an examination of surrounding soft tissue involvement and the detection of skull base inflammatory involvement or intracranial complications.[13] Al-Noury and Lotfy evaluated 18 cases of MOE. An examination of temporal bone CTs disclosed persistent bone erosion in all 18 patients. Moreover, temporal bone MRIs showed that 60% of patients had soft tissue alterations and 33% had bone marrow anomalies that persisted for 1 year.[14] Cherko et al, used MRI with diffusion weighted imaging (DWI), for a radiological follow-up of patients with MOE.[15] Other reports have indicated that scintigraphy with radiopharmaceuticals, such as Gallium-67 citrate, or leukocyte labeling with HMPAO-Tc99 or Sulesomab-Tc99, showed high diagnostic specificity for MOE; in some cases, these approaches were also used in clinical follow-ups.[1,16,17]

Currently, specific guidelines for MOE management and treatment have not been established in the literature. Based on our experience, and considering the data available in the literature, we propose a diagnostic-therapeutic flow-chart for MOE treatment (Figure 2). As suggested previously, the first therapeutic approach should be medical treatment. Patients typically receive strict diabetes mellitus monitoring and treatment with a high oral dose of fluoroquinolones, such as ciprofloxacin. Fluoroquinolones are useful, due to their low toxicity and high ability to reach bone tissue. However, microbial resistance to those classes of antibiotics has been described; consequently, many authors have proposed carbapenem or third-generation cephalosporins, such as ceftazidime or cefditoren.[5,18,19] Long-term use of aminoglycosides can lead to nephrotoxicity and ototoxicity.[20] However, voriconazole or amphotericin B has been suggested for treating overlapping *Aspergillus* infections.[6,10 ,12] An emerging problem is the appearance of antibiotic resistance in *Pseudomonas* spp. and other Gram-negative bacteria. Thus, antibiotic use should be carefully managed.

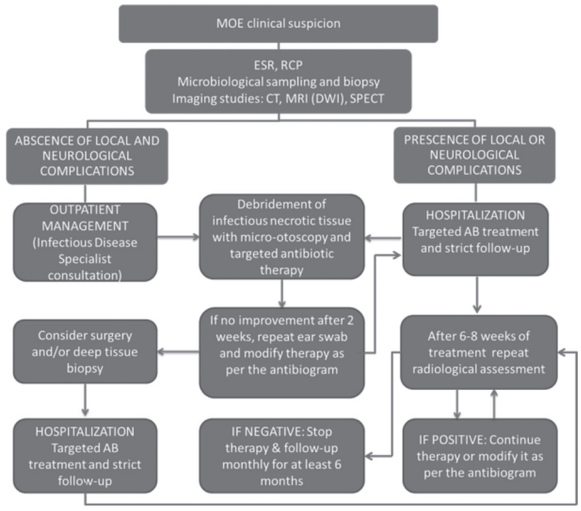

Figure 2
Proposed diagnostic and therapeutic flow-chart for patients with malignant otitis externa (MOE)

When the initial clinical and neuroradiological evaluations (Figure 2) produce findings of local or neurological complications, prompt hospitalization is necessary to facilitate daily micro-otoscopic debridement and a strict clinical follow-up (in particular, monitoring glycemia). When no improvement is observed after 2 weeks of targeted antimicrobial therapy, the ear swab should be repeated, and based on analytical findings, the antimicrobial treatment should be adjusted. Furthermore, after 6/8 weeks from the initial assessment, another neuroradiological assessment should be performed (Figure 2). The role of hyperbaric therapy in MOE management remains to be defined; however, it should be used in combination with antimicrobial therapy.[21] According to the most recent findings in the literature, surgery has limited value (Figure 2); some authors have indicated that surgery promoted the spread of infection through fascial and vascular planes or to healthy bone, which worsened the prognosis.[4,6] A surgical approach is indicated in cases of antimicrobial therapy failure, deep local debridement, cartilaginous/bony sequestrum removal, abscess drainage, or suspected neoplastic lesions (i.e., ear canal squamous cell carcinoma).[22,23] Therefore, in our experience, the management of MOE should always involve an infectious disease specialist and a neuroradiologist. Both can play important roles in informing a correct diagnosis and evaluating treatment responses, in collaboration with the ENT specialist.

We recommend that clinical randomized studies of large series should be performed in the near future to clarify the best medical and surgical approaches for treating this insidious pathology.

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