



Malignant External Otitis: What the Diabetes Specialist Should Know—A Narrative Review

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Received: January 18, 2023 / Accepted: February 24, 2023 / Published online: March 10, 2023
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ABSTRACT

Aims: Malignant external otitis (MEO) is a special type of external otitis associated with extensive inflammation and osteomyelitis. It is believed to originate from the external auditory meatus and advance regionally to the soft tissues and the bone, eventually involving the skull base. *Pseudomonas aeruginosa* and diabetes mellitus are factors commonly involved in the pathogenesis of MEO. Although its treatment has changed considerably during the last decades, morbidity and mortality of the disease remain high. Our aim was to review basic aspects of MEO, a disease unknown until 1968, which attracts great interest among Ears, Nose and Throat (ENT), diabetes and infectious diseases specialists.

Methods and Results: In this narrative review we mainly include relevant papers written in English or with an English abstract. We searched PubMed and Google Scholar, using the keywords malignant external otitis, malignant otitis externa, necrotizing external otitis, skull base osteomyelitis, diabetes mellitus and surgery up to July 2022. Some of the most recent articles, with specific references to earlier articles and a book reference regarding the pathophysiology, diagnosis and treatment of MEO and its relationship to diabetes mellitus, were included.

Conclusion: MEO is not an uncommon disease and is principally treated by ENT surgeons. Nevertheless, diabetes specialists should be aware of the disease presentation and management, since they will often encounter patients with undiagnosed MEO or will need to manage glucose levels in patients hospitalized with the disease.

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Keywords: Diabetes mellitus; Malignant external otitis; Malignant otitis externa; Necrotizing external otitis; Skull base osteomyelitis; Surgery

Key Summary Points

Malignant external otitis is an aggressive type of external otitis, usually involving *Pseudomonas aeruginosa*, leading to osteomyelitis of the skull base.

Diabetes mellitus and immunodeficiency have been traditionally linked to malignant external otitis, but it can also appear in healthy individuals.

Ear pain, otorrhea and edema of the external auditory meatus are commonly seen in these patients.

Computed tomography (CT) and magnetic resonance imaging (MRI) scans along with technetium and gallium scans are common imaging modalities used in diagnosis and follow-up of malignant external otitis.

Antipseudomonal antibiotics and efficient glycemic control currently constitute the gold standard in management of malignant external otitis, while surgery should be considered in special cases.

INTRODUCTION

Malignant external otitis (MEO)—or malignant otitis externa or necrotizing external otitis—is an aggressive type of external otitis which shows an outspread of inflammatory activity towards the soft tissues of the external auditory meatus and bone of the skull base and presents severe morbidity and mortality [1]. Use of the term malignant is unsuitable, since it does not describe the development of cancer but more the rapid local spread of the inflammation to healthy tissues. The first report of the disease is attributed to Toulmouche in 1838, while the term ‘malignant otitis externa’ was first used by Chandler in 1968 [1, 2].

Incidence rates of MEO vary with a population-based study held in Taiwan reporting 2.24

per million person-years of observation and another in Spain reporting 1.3 per million inhabitant per year [3]. Individuals < 18 years old present with a very low incidence of the disease [3]. MEO is more common in males than females (1.45 males:1 female) [4].

Despite the advances in the treatment of MEO, incidence rates of 10–20% have been published [5], with a more recent study from the US reporting an overall mortality of 2.5% during the initial hospitalization [4]. Existing diabetes and poor glycemic control are associated with longer hospitalization, increased healthcare costs and mortality in this patient category [3].

Our Ear, Nose and Throat (ENT) Department has had long experience in handling these patients. Specifically, 11 cases of patients with MEO presented in 1977, one of the largest case series at that time. At this time quinolones were not yet widely used and these patients were treated with surgery and other antibiotics, with the report of five deaths [6]. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

PATHOPHYSIOLOGY

As implied by its name, the disease is believed to originate from the external acoustic meatus and can evolve from cellulitis to chondritis, periostitis and eventually osteomyelitis, thus involving the bone of the skull base and the cranial nerves arising from the skull base foramina. Therefore, the term ‘skull base osteomyelitis’ is also used in its final stages [7]. MEO progresses from the external auditory meatus through the fissures of Santorini and then through fascial and vascular planes and can reach the dural sinuses and petrous apex. Except for the stylomastoid foramen and the facial nerve, which can be affected, the disease can also reach the jugular foramen and thus the vagus, glossopharyngeal and accessory nerves. The inflammation can reach the hypoglossal canal and nerve and finally the cavernous sinus with its structures [8].

Pseudomonas aeruginosa is predominantly involved in cases of MEO with a frequency of 50–90% of all cases [1]. *Proteus mirabilis* and

other *Proteus* species, *Staphylococcus epidermidis* and *Klebsiella* species are also commonly implicated bacteria. Fungi, such as *Aspergillus fumigatus* and *Candida* species have also been isolated in cultures. Methicillin-resistant *Staphylococcus aureus* (MRSA) should also be suspected in patients without diabetes [1]. During the last years, however, an increase in culture-negative patients has been reported. This could be a result of modern treatment protocols, which demand an immediate prescription of antibiotics upon patient presentation rather than a shift in the involved bacteria [9].

MEO and advanced age have been traditionally linked to elderly patients with diabetes. Another patient group at higher risk of MEO is those with immunodeficiencies, such as patients with human immunodeficiency virus (HIV) or cancer. In these patients the symptoms of inflammation are suppressed [10]. A high index of suspicion should be held concerning immunodeficient individuals with external otitis not responding to antibiotics. Radiation therapy of the head and neck area has also been linked to MEO, through chronic inflammation and necrosis of the soft tissues and bone [11].

According to a recent work by Sideris et al., patients with MEO not suffering from diabetes mellitus or immunosuppression constitute a distinct category. Specifically, MEO can present in these patients at a younger age and responds better to antibiotics. Additionally, a shorter duration of hospitalization is needed. The importance of high clinical suspicion for MEO in patients with external otitis not responding to antibiotics is highlighted [12].

DIAGNOSIS

MEO most commonly presents with non-resolving nocturnal ear pain, followed by exudate, hearing impairment and temporomandibular joint. Otoloscopic findings include edema of the external ear canal with granulation tissue at the osseocartilaginous junction and more rarely only edema or aural polyps [13].

Palsies of the cranial nerves on the side of MEO are not unusual. Clinical evaluation

should include examination of the cranial nerves, specifically the facial (VII), glossopharyngeal (IX), vagus (X), accessory (XI) and hypoglossal (XII) nerves. The facial nerve is most commonly while the hypoglossal nerve most rarely affected [14]. It has been reported that facial nerve paralysis increases mortality by 50% [15]. Facial nerve paralysis is considered to occur in 75% of individuals with *Aspergillus* infection, while only in 34% of those with *Pseudomonas* infection [16].

Blood inflammatory markers, such as white blood cell count, erythrocyte sedimentation rate and C-reactive protein (CRP), should be obtained. The two latter measurements are usually elevated, while the white blood cell count usually is normal or slightly elevated [17]. The inflammatory markers can be used for disease monitoring and correspondence to treatment [18]. Diabetes tests, such as blood glucose and HbA1c levels, are very important, since sufficient glucose and inflammation controls are milestones in the treatment of the disease. Patients without a known history of diabetes should, nevertheless, be tested. Fasting plasma glucose and glucose tolerance tests should be performed after reduction of the inflammation. Renal and liver function should also be monitored.

Next, culture of ear secretions should be obtained before initiation of antibiotics to assess both the pathogen and its resistance to treatment. A biopsy of the granulation tissue should also be performed for differential diagnosis among MEO, tumor and cholesteatoma [19]. Culture of a superficial swab of the external auditory meatus is most commonly conducted, while deep biopsies can be selected in cases of refractory MEO or probable fungal infections [20].

Diagnosis of MEO is principally clinical and relies on the major diagnostic criteria, which we will discuss later [21]. CT and MRI are currently predominantly used in the management of MEO, replacing the standard nuclear scans [22]. High-resolution CT scan of temporal bone and MRI assist in assessing the extent of disease to bone and soft tissue, respectively. CT specifically helps identify small cortical erosions, further bone involvement, osteomyelitis, extent of

osseous involvement and intracranial spread of the disease [7]. It is also useful in calculating the Peleg score and thus evaluating severity of MEO and type of treatment [23].

Technetium (Tc-99) bone scan is a radio-labeled scan based on the capability of Tc-99 to bind to osteoblasts, uncovering elevated osteoblastic activity, which occurs in osteomyelitis. Its significance lies in its high sensitivity to diagnose bone involvement. It has good specificity but is not suitable for follow-up since it can remain positive long after disease resolution [21]. Okpala et al. suggest a diagnostic protocol with CT as the initial imaging modality to reveal osteomyelitis of the skull base. If positive, we should proceed with treatment of MEO, while if negative, a Tc-99 bone scan should be conducted. The latter should lead to the eventual diagnosis or ruling out of osteomyelitis [24].

Gallium (Ga-67) is absorbed by reticular endothelial cells and macrophages and is sensitive in indicating the presence of inflammation. Single-photon emission computed tomography (SPECT) bone scan with Ga-67 is the investigation of choice in monitoring MEO to evaluate response to treatment and possible recurrence. SPECT imaging with Tc-99 or Ga-67 increases anatomical localization of the disease compared to planar scintigraphy [24].

However, Moss et al. report that Tc-99 and Ga-67 scintigraphy has low specificity and spatial resolution, while its ability to diagnose disease resolution is not proven. Thus, routine use in diagnosis of MEO is not supported [25]. F18-fluorodeoxyglucose positron emission tomography/computed tomography (F18-FDG-PET/CT) is an alternative to the conventional bone scintigraphy techniques and is considered reliable for diagnosis, localization and decision-making regarding therapy discontinuation in patients with MEO. It can be used in both diagnosis and follow-up of the disease [26]. Indium-111-labeled white blood cell imaging is not reliable in ruling out MEO [24].

According to Cohen and Friedman, establishing the diagnosis of MEO relies on identification of the following major criteria, which must all be present: otalgia, purulent otorrhea, edema and granulations of the external

auditory meatus, microabscesses in cases of surgical management, pathological technetium 99 bone scan (99Tc) and failure of local therapy after more than a week. Minor criteria include a pathological radiograph, *Pseudomonas* growth in culture, diagnosis of diabetes mellitus, cranial nerve involvement and a debilitating condition. Minor criteria alone do not suffice for diagnosis [21].

CLASSIFICATION

The Carney clinicopathological classification of MEO is a useful tool (Table 1). In stage 1, there is clinical evidence of MEO with inflammation of soft tissues beyond the external acoustic meatus and a physiological 99Tc bone scan. In stage 2, soft tissue inflammation spreads beyond the external acoustic meatus, but with a pathological 99Tc bone scan. Stage 3 is similar to stage 2, but with cranial nerve palsies (3a single, 3b multiple nerve palsies). Stage 4 is accompanied by intracranial complications, such meningitis [27].

Computed tomography is very important because, except for assistance in diagnosis and information on disease outspread and small cortical lesions, it can also help predict the clinical course and severity of the MEO according to Peleg et al. The Peleg is a 4-point score, as seen in Table 2, consisting of 1 point for diabetes mellitus type 1 and 1 point for involvement of one of each structure on CT: temporal bone, skull base bone and temporomandibular joint. Thus, patients with a score of 0–2 are considered non-severe patients, while those with a score of 3–4 severe patients [23].

Soudry et al., in an effort to identify patients with aggressive MEO early, defined the following criteria: bilateral disease, cranial nerve involvement and CT findings. The latter include erosions of the infratemporal fossa and base of the skull and involvement of the nasopharynx. It is also important to diagnose and properly treat fungal infections [28].

A more recent stratification protocol by Stevens et al. introduces nine disease variables. Specifically, it contains four clinical variables, namely facial nerve palsy, relapse of MEO, need

Table 1 Carney clinicopathological staging

Stage 1	Clinical evidence of MEO with inflammation of soft tissues beyond the external acoustic meatus and normal 99Tc bone scan
Stage 2	Clinical evidence of MEO with inflammation of soft tissues beyond the external acoustic meatus AND positive 99Tc bone scan
Stage 3	Clinical evidence of MEO with inflammation of soft tissues beyond the external acoustic meatus AND positive 99Tc bone scan AND cranial nerve involvement
Stage 3a	Single cranial nerve palsy
Stage 3b	Multiple cranial nerve palsies
Stage 4	Meningitis, sinus thrombosis, empyema and brain abscess

Table 2 Peleg stratification

Peleg score	Points
Diabetes mellitus type 1	1
Temporal bone involvement	1
Skull base involvement	1
Temporomandibular joint involvement	1

for surgery and fungal infection, and five radiographic variables, namely temporomandibular joint lesions, infratemporal fossa erosion, tegmen tympani erosion, nasopharynx and intracranial complications. Severe MEO is diagnosed when: (1) facial nerve involvement is present, (2) at least two clinical variables are present, (3) at least two radiological variables are present and (4) at least one clinical and one radiological variable are present. In cases of severe MEO, there is higher morbidity and usually need for surgical treatment [29].

TREATMENT

Several years ago, before the introduction of antipseudomonal antibiotics in the treatment of MEO, surgery was considered the main treatment modality with a mortality of 67% [30]. This has entirely changed, however, since the introduction of antibiotics, while the role of surgery remains controversial.

It is very important to diagnose the disease in the early stages, because it progresses and spreads over time, greatly affecting the skull base with high morbidity and mortality. Therefore, family physicians treating patients with external otitis should be suspicious of MEO when nocturnal pain and symptoms persist despite treatment with antibiotics and when granulation tissue of the external auditory meatus is present. A bacterial culture should be obtained before prescription of antibiotic agents, and the patient should be referred to an ENT surgeon if the symptomatology persists for more than a week [31].

Currently, the standard of care includes antibiotics either at home or during hospitalization in more severe cases. Usually topical and systemic fluoroquinolones are administered. Ciprofloxacin has been widely used during the last years because of its antipseudomonal activity, but patients who present ciprofloxacin resistance are increasingly common. In such cases an antibiogram should provide answers, and it is not rare to combine an aminoglycoside with a semisynthetic penicillin against multidrug-resistant organisms [1].

Duration of antibiotic administration is not clearly defined in the literature because of the different factors affecting the disease. It can vary from 4 to 59 weeks with an average of 15 weeks. Gallium scan has been traditionally considered the imaging of choice for follow-up of MEO, and it has been proposed that antibiotics should be discontinued about 4 weeks after a negative scan [17, 32]. Erythrocyte sedimentation rate is usually used for follow-up of the disease. Its normalization usually indicates resolution of MEO. Normalization of nocturnal ear pain appears to be a reliable indicator of resolution, too [17].

Several surgical operations have been described in this patient category. Local debridement of the external ear canal is still largely carried out and can be accompanied by deep tissue biopsy. Other procedures, which conducted are currently under certain circumstances, are facial nerve decompression, canal wall-up or canal wall-down mastoidectomy and petrosectomy. The selection of the suitable surgical modality is determined mostly by the clinical and radiographic findings and the response to antibiotics [33].

On one hand, surgery can help reduce topical infective load, debride necrotic tissue and facilitate healthy tissue formation with better vascularization [34]. On the other hand, however, it is believed to provoke disease progression through fascial and vascular planes; thus, open surgery, such as decompression in cases of facial nerve paralysis, should be avoided. Indeed, the role of surgical treatment of MEO has been revised and is no longer considered vital [35].

According to a recent review, antibiotics have proven to be the gold standard for MEO patients, while the role of extensive surgical treatment has significantly diminished during the last years. Antipseudomonal drugs are commonly implemented, with an increase in the use of ceftazidime, but a decrease of ciprofloxacin. Nevertheless, ciprofloxacin remains the most widely used antibiotic, with ceftazidime, piperacillin-tazobactam and meropenem following. Although MEO has been better described and understood, a significantly diminished cure rate has been observed since 2009, while disease-specific mortality has not changed [9].

According to Peled et al., surgery should be considered in certain conditions. Non-responsiveness to long-term antibiotic use (at least 3–4 weeks) in cases of resistant or undiagnosed bacteria in cultures, lack of proper antibiotic agents against specific microorganisms or diabetic microangiopathy is the main indication for surgery. Clinical findings along with erythrocyte sedimentation rate and CRP should be considered to assess unresponsiveness to treat-

ment. Surgical treatment is also indicated when aggressive or severe disease, as defined by the above-mentioned stratification systems, is present. Additionally, sterile deep tissue cultures combined with poor response to conservative treatment could be a relative indication for surgery [33].

Analgesics are an important factor in treating MEO, but they should normally be administered only for a few days, e.g., the first 5 days, since regression of pain should be monitored during the course of the disease and is an indicator of disease resolution [17].

According to a systematic review, hyperbaric oxygen therapy could be a significant adjunct in the treatment of refractory or chronic cases of MEO, particularly in patients with diabetes mellitus. As already mentioned, patients with diabetes exhibit significant factors that contribute to MEO development like poor white blood cell chemotaxis and diabetic microangiopathy, which lead to tissue hypoxia. Hyperbaric oxygen therapy, on the other hand, is considered to ameliorate oxygen partial pressure in the site of infection, increase bone and soft tissue healing and improve oxygen-mediated leucocyte function [36].

Different complications of MEO should receive more targeted treatment. For example, temporomandibular joint inflammation, which is rare and considered to have poor prognosis, can be treated with skeletal muscle relaxants for symptom relief [17]. Facial nerve palsy as an indication for surgery is debatable, since according to several authors, many cases are associated with good response to conservative treatment. Thus, it is important to evaluate the overall clinical picture of the patient [33].

Overall, use of classification systems, e.g., the Peleg score, to classify patients as non-severe and severe could be implemented to decide proper treatment. Non-severe patients can be treated mainly with antibiotics and minimal surgery of the external acoustic meatus when needed. Severe patients should receive an aggressive therapy with multiple antipseudomonal antibiotics and early surgical debridement of the affected structures [23].

DIABETES AND MEO

As already mentioned, patients with diabetes are at risk of MEO. This specific group presents microangiopathic changes in the external auditory meatus and hindering of the white blood cell chemotaxis, which leads to vulnerability to infections [9]. Specifically, in a study by Guerrero-Espejo et al., 74.6% of patients with MEO had diabetes, while the disease predominantly affected patients > 84 years of age [37]. In a population-based case control study, patients with MEO had a prevalence of diabetes mellitus of 54.8% and an adjusted odds ratio of diabetes for patients with MEO versus controls of 10.07 (95% CI) [3]. In an 11-year analysis of 8300 patients in the US, 55.1% had concomitant diabetes mellitus, while interestingly elderly patients, who are considered the main risk group with diabetes, constituted only 22.7% of cases [38].

Hyperglycemia and glucose variability in hospitalized patients with and without diabetes are linked to a notable increase in morbidity, mortality and health-care costs. Insulin therapy is recommended as the cornerstone of inpatient pharmacological treatment of MEO. Most clinical guidelines recommend stopping oral antidiabetic drugs during hospitalization [39]. However, continuation of oral glucose-lowering medications is applied in some hospitalized patients in different countries. This is based on a variety of clinical trials that suggest that non-insulin antidiabetic agents, alone or in combination with basal insulin, can be used to achieve efficient glycemic control in selected populations. In stable patients who are adequately controlled on their outpatient regimen and are able to eat, oral agents may be continued [40].

A plethora of treatment options for diabetes exist. Modifications to diet or medication regimens may be used to improve high blood glucose level. Basal insulin or a basal plus bolus insulin correction regimen is the preferred treatment for noncritically ill hospitalized patients with inadequate oral intake. An insulin regimen including basal, prandial and correction components is the preferred choice for

patients with sufficient nutritional intake. Insulin therapy should be initiated for the treatment of persistent hyperglycemia at the level of ≥ 180 mg/dl (10.0 mmol/l, confirmed on two occasions), targeting a glucose range of 140–180 mg/dl (7.8–10.0 mmol/l) for most critically ill and hospitalized patients. In the critical care setting, continuous intravenous insulin infusion is the best option for adequate glycemic control [41]. Before intensive care unit discharge, stable patients can be transitioned to subcutaneous insulin regimens [39].

MEO, although rarer, presents similarities to the pathogenesis of and population involved in diabetic foot osteomyelitis. Specifically, microangiopathy and neuropathy are considered to play a key role in both. It is interesting to remember, however, that MEO is usually monomicrobial, while diabetic foot osteomyelitis is polymicrobial, and that an ear swab culture usually suffices for MEO, while in the latter bone biopsy is needed for diagnosis [42].

CONCLUSIONS

MEO is an aggressive type of external otitis leading to osteomyelitis of the skull base bone. The usual microorganism involved is *Pseudomonas* species, and it usually affects individuals with diabetes mellitus. Treatment of the disease has changed over the years, today following conservative treatment modalities with antibiotics and conducting surgery under special circumstances. MEO is a rare but fatal disease, and the specialists involved in its diagnosis and treatment, namely ENT surgeons and diabetes specialists, should be aware of it.

ACKNOWLEDGEMENTS

Funding. No funding or sponsorship was received for this study or publication of this article.

Authorship. All named authors meet the International Committee of Medical Journal

Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Author Contributions. The idea for this paper was conceived by Christos Tsilivigkos and Eleftherios Ferekidis. The first draft of the manuscript was written by Christos Tsilivigkos and Konstantinos Avramidis, which was read and edited by Eleftherios Ferekidis and John Doupis. All authors approved the final version of this manuscript.

Disclosures. Christos Tsilivigkos, Konstantinos Avramidis, Eleftherios Ferekidis and John Doupis have nothing to disclose.

Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

Data availability. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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