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Evaluation of the clinical and radiological features of patients with Malignant otitis externa (MOE)

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Abstract

Introduction Malignant otitis externa (MOE) is a life-threatening infection of the external auditory canal and temporal bone.

Objective This study is designed to identify the clinical features, predisposing factors, radiological findings, complications, diagnoses, and management of MOE patients.

Study design Retrospective cross-sectional study.

Setting Loghman-e-Hakim Hospital, Tehran, Iran.

Methods The study included 40 patients diagnosed with MOE from 2011 to 2023. The data extracted from medical records included demographic data, clinical signs and symptoms, radiological findings, laboratory data, predisposing factors, complications, treatments, and outcomes. Out of 37 patients, 21 were followed up.

Results The study found that the mean age of patients was 62.24 ± 11.44 years, with 62.2% being male. Otalgia and otorrhea were the most commonly reported symptoms, and mastoiditis was the most common radiological finding. Bone erosions and osteomyelitis were other important complications. Vascular complications were also observed in 7 patients. The study also found that most patients had underlying conditions such as diabetes mellitus, hypertension, ischemic heart disease, and renal disease. One patient passed away during hospitalization, while others improved and were discharged. Then, at follow-up, 11 patients died, mainly due to the progression of underlying disorders including cardiac, and renal manifestations.

Conclusion Based on our findings, although MOE most commonly occurs in poorly-controlled diabetic or immunocompromised patients, it can also occur in individuals without known conditions. Furthermore, increasing the age and severity of DM could lead to more complications. In terms of medical therapy, coverage of gram-positive bacteria and an antipseudomonal regimen would be an effective treatment.

Keywords Malignant otitis externa, Diagnoses, Management

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Introduction

Malignant otitis externa (MOE) is a rare and aggressive infection affecting the external auditory canal (EAC) and temporal bone, posing significant morbidity and mortality risks. Although an array of bacteria and fungi may be involved in the etiology of MOE, *Pseudomonas aeruginosa* appears to be the primary contributing to the development of the disease [1, 2]. However, *Staph aureus* may be more common than *Pseudomonas* in chronic kidney disease. Information regarding the incidence of the disease is controversial owing to confined epidemiological data. Some studies have reported an increase in MOE incidence in certain, whereas another study showed a decline [2–4]. The most prevalent signs and symptoms associated with MOE include otalgia, otorrhea, headache, and hearing loss. The disease may progress beyond affecting the soft tissue and cartilage, potentially leading to serious damage to the bones as well as other complications resulting in a rise in mortality and morbidity [5, 6]. MOE is often associated with underlying conditions such as diabetes, immunosuppression, HIV infection, and a history of head and neck radiotherapy [2, 7]. Diagnosis involves clinical, laboratory, and imaging findings, while treatment typically includes long-term antimicrobial therapy and, in severe cases, surgery [2, 8, 9]. Some studies showed a low mortality rate and also an association of age, gender, comorbidities, and cranial nerve involvement with unfavorable outcomes [10, 11]. However, Loh et al. indicated a higher mortality rate and Sylvester et al. found no relation between comorbidities including DM with mortality [12, 13]. Due to the contentious findings regarding the complications, comorbidities, mortality, and outcomes among prior studies, there is a necessity to provide further research and additional evidence. This study aims to contribute to the understanding of MOE by retrospectively evaluating 13 years of admitted patients with MOE in Loghman-e-Hakim Hospital, Tehran, Iran, to identify clinical features, predisposing factors, complications, diagnoses, management, and outcomes.

Materials and method

This study intended to investigate patient characteristics, clinical signs and symptoms, radiological findings, laboratory data, predisposing factors, complications, treatments, and outcomes of patients with MOE, by conducting a retrospective study of patients diagnosed with MOE by expert specialists from 2011 to December 2023 in a referral center of Otorhinolaryngology and Infectious Diseases. These specialists diagnosed MOE based on disease resistance to the treatment (continued symptoms of the disease despite treatment of otitis externa) along with compatible findings on examination and

imaging. An initial search of medical records registered in the hospital's database yielded a total of 15 cases with MOE. A comprehensive investigation of the 722 otitis and mastoiditis cases since 2018 was carried out. Following a thorough evaluation and the omission of duplicate files, 40 cases with MOE were identified. Our study was approved by the Research Ethical Committee of Shahid Beheshti University of Medical Sciences (IR.SBMU.RETECH.REC.1402.211).

The following data was obtained from medical records after identifying MOE cases: 1) Demographic data (age, sex, site of infection), 2) Clinical signs and symptoms (otalgia, otorrhea, hearing loss, headache, tinnitus, cranial nerve involvement, granulation tissue, and fever), 3) Radiological findings (mastoiditis, bone erosion, TMJ involvement, and soft tissue involvement), 4) Laboratory data (hemoglobin, total leukocyte count, platelet count, ESR, CRP, FBS, HbA1C, BUN, and Creatinine), 5) Underlying disease (including DM, immunosuppression, cancer history, HIV), 6) Complications (bone involvement, otitis media, and tympanic involvement), 7) Treatments (medical and surgical treatment), 8) Outcome (LOS, relapse, and mortality due to MOE). The extraction process was performed and rechecked by three authors to ensure reliability and minimize selection and measurement bias.

All available radiological documentations of the patients were re-examined by an expert radiologist to find any of the following: unilateral or bilateral external otitis, mastoiditis, osteomyelitis or bony erosion (sphenoid, occipital, temporal, and mandibular), cellulitis (infratemporal, temporal, parapharyngeal, buccal, and masticator), temporomandibular joint (TMJ) arthritis, cholesteatoma, internal carotid artery (ICA) involvement (vasculitis, narrowing, or complete occlusion), ipsilateral or contralateral cerebrovascular accident (CVA), central vein thrombosis of jugular vein and/or transverse, sigmoid, cavernous sinus, orbital involvement, dural involvement, brain involvement, abscess formation (parapharyngeal, infratemporal, and brain), and necrosis (parapharyngeal, infratemporal, and masticator). The patients underwent CT scan with Toshiba Activion device. Axial images with 0.5 mm slice thickness and without IV contrast were obtained in the bone window and reformatted in the coronal plane. Neck magnetic resonance imaging with and without Gadolinium were performed for patients additionally with magnetom Amira Siemens corporation (slice thickness: 3 mm, matrix: 256*218, FOV: 190*190).

For patient follow-up, we conducted in-person visits, electronic medical records, and phone calls for available patients. At this stage, the following questions were answered: 1) Is the patient alive? 2) In case of death, was it due to MOE? 3) Are there any persistent symptoms? 4) Has the patient experienced a relapse?

Of all 40 cases, we could establish contact with 21 patients. The extracted data from medical records as well as information retained through the phone calls were analyzed. computer software IBM SPSS version 26 (Armonk, NY, USA: IBM Corp) was used to perform the statistical analyses. Patient characteristics were expressed using the frequencies, percentages, and Mean±Standard deviation (SD). Independent sample *t*-tests, and cross-tabulation (Pearson's chi-square and Fisher's exact test) were used for finding the associations. Logistic regression was used for the analysis of the risk factors. *P*-value < 0.05 was considered as statically significant.

We also searched the literature in PubMed/MEDLINE. Fifty-four selected articles were reviewed in the ((discussion and literature review)) section.

Results

Demographic data

A total of 40 patients were included in this study. The mean±SD age of the patients was 61.85±11.08 with the range of 35-81 years old. The majority of cases (26 patients) were over 60 years of age. However, only four cases involved people under 40 years of age. The

frequency of male and female cases was 24 (60%) and 16 (40%), respectively. After stratification of patients according to the infection site, right and left ear infection was observed in 18 (45%) and 19 (47.4%) patients. Three cases (7.5%) represented infection in both ears. Examination of any possible associations between these variables demonstrated that neither of them had a significant association with mortality or MOE relapse (Table 1).

Symptoms and signs

Of all clinical signs and symptoms, persistent otalgia and otorrhea were the most commonly reported symptoms, experienced by all and 32 (80.0%) of patients respectively. To a lesser extent, hearing loss and headache were reported in 21 (52.5%) and 14 (35%) patients, respectively. Tinnitus was only reported in 10 (25%) patients. As signs of the disease, granulation tissue was present in 9 (22.5%) and fever was detected in 6 (15%) patients on admission. Cranial nerve involvement was present in 13 (27%) patients with only the facial nerve (CN VII) being affected. Symptoms lasted for 13.13±12.54 weeks

Table 1 Demographic features, clinical findings, radiologic findings, comorbidities, and complications results and their association with relapse of MOE, mortality, and hospitalization. *P*-value < 0.05 is statistically significant

Variables	Descriptives (Y/N)	Relapse (<i>p</i> -value)	Mortality (<i>p</i> -value)	LOS* (<i>p</i> -value)
Demographics				
Age (mean)	61.85 ± 11.44	0.486	0.230	0.738
Sex	M/F: 24/16	0.664	0.278	0.802
Symptoms & Signs				
Otalgia	40/0	-	-	-
Otorrhea	32/8	0.891	0.455	0.536
Headache	14/26	0.517	0.901	0.675
Hearing loss	21/19	0.217	0.150	0.528
Tinnitus	10/30	0.319	0.261	0.593
Immune system status				
Cancer	1/39	-	-	0.299
Transplant	2/38	0.3	0.522	0.176
Underlying disorders				
DM	35/5	0.891	0.124	0.726
HTN	22/18	0.217	0.407	0.336
IHD	15/25	0.129	0.071	0.173
Renal disease	9/31	0.483	0.134	0.341
ESRD (Dialysis)	3/37	0.479	0.466	0.510
Complications				
CN involvement	13/27	0.517	0.901	0.032
Otitis Media	18/22	0.455	0.407	0.734

Patients with CN involvement are hospitalized for more than 20 days on average

Abbreviations: LOS Length of stay, DM Diabetes mellitus, HTN Hypertension, IHD Ischemic heart disease, CN Cranial nerve

*A cutoff of 20 days is used to analyze LOS

ranging from 1–48 weeks in total, including admission and treatment.

The study also revealed a significant association between cranial nerve involvement and a length of stay of more than 20 days ($p = 0.034$). However, there was no significant association between symptom duration and disease mortality or relapse (Table 1).

Radiological findings

CT scan and MRI were two modalities used to study these patients. Among a total number of 25 patients with available radiology documents, 11 patients underwent CT scan only and 14 patients underwent both CT scan and MRI.

Table 2 Description of radiologic findings in detail

Findings	CT scan	MRI
Mastoiditis	25/25	
Unilateral (right)	20/25	
Bilateral	5/25	
TMJ involvement	21/22	
Bone erosion	17/20	
Occipital	1/20	
Temporal	2/20	
Mandibular	1/20	
Temporal + Mandibular	10/20	
Temporal + Sphenoid	1/20	
Temporal + Mandibular + Occipital	1/20	
Temporal + Mandibular + Sphenoid + Occipital	1/20	
None	3/20	
Osteomyelitis	16/23	
Temporal	3/23	
Mandible	3/23	
Temporal + Mandible	6/23	
Mandibular + Occipital	1/23	
Temporal + Sphenoid + Occipital	2/23	
Temporal + Mandible + Sphenoid + Occipital	1/23	
None	7/23	
Vascular involvement		7/14
Cavernous vein thrombosis		1/14
Jugular vein thrombosis		2/14
ICA narrowing		2/14
Jugular vein thrombosis + ICA narrowing		1/14
Cavernous vein thrombosis + ICA narrowing + ICA vasculitis		1/14
Meningeal involvement		5/14
Necrosis		4/14
Parapharyngeal		2/12
Infratemporal		1/12
Parapharyngeal + Infratemporal		1/12

Abbreviation: JVT Jugular vein thrombosis, CVT Cavernous vein thrombosis, ICA Internal carotid artery, LOS Length of stay, MOE Malignant otitis externa

Among the radiological findings of the patients, mastoiditis was the most common finding, followed by TMJ involvement. Herein, we described the findings of these modalities in detail (see also Table 2).

CT scan

The modality assessed the presence of external otitis, mastoiditis, bone erosion, osteomyelitis, temporomandibular joint (TMJ) arthritis, and cellulitis among the patients.

MRI

The imaging modality was used to evaluate the presence of various complications in 14 patients. Vascular involvement, meningeal involvement, and necrosis were shown in Table 2. Also, the individualized findings in these patients were documented in Table 3.

Subsequent analysis did not reveal any significant association between the radiological findings and the mortality or relapse of MOE (Table 1). However, in patients over 55 years old, osteomyelitis was found in more than one bone ($p = 0.046$). Additionally, an initial FBS of over 300 mg/dl and HbA1C of over 8.5 were significantly associated with osteomyelitis in more than two bones ($p < 0.05$). Figure 1, 2, and 3 are representative images of CT scan and MRI of the patients.

Laboratory results

Laboratory data of patients were documented in Table 4.

Our analysis demonstrated that elevated ESR level was associated with higher mortality (p -value=0.015) and elevated CRP level was correlated with higher relapse of the disease (p -value=0.049). Further analysis demonstrated that no significant association between laboratory findings and mortality or relapse of the disease Table 4.

Underlying conditions

Of 40 patients, 35 (87.5%) were known cases of poorly controlled diabetes mellitus (DM), 22 patients (55%) had hypertension (HTN), 15 (37.5%) had ischemic heart disease (IHD), and 9 (22.5%) had a past medical history of renal disease. Of these renal patients, three were known cases of end-stage renal disease (ESRD) and underwent dialysis. Four patients (10%) had none of the mentioned comorbidities. Ten patients (25%) had one, and 13 patients (32.5%) had two comorbidities at the same time. Also, six (15%) patients had three, and seven patients (17.5%) had all of the four above-mentioned comorbidities.

Female patients are more likely to develop MOE without any comorbidity, whereas the relative count of male patients with all of the mentioned comorbidities is more than females (Figure 4).

Table 3 Individualized findings of 14 patients undergoing MRI and their outcome

PATIENTS NO	Osteomyelitis				Vascular complications				Meninges			Outcome			
	Temporal	Mandible	Sphenoid	Occipital	JVT	CVT	ICA vasculitis	ICA narrowing	Meningeal complication	Parapharyngeal	Infratemporal	Abscess	LOS	Relapse	Death
1	Yes	Yes	Yes	Yes		Yes	Yes		Yes	Yes			15	No	No
2	Yes		Yes	Yes	Yes			Yes	Yes	Yes	Yes		20		No
3	Yes		Yes	Yes	Yes								25		No
4	Yes	Yes							Yes		Yes		7		No
5	Yes	Yes			Yes								24		No
6	Yes	Yes											21	No	No
7		Yes		Yes				Yes					20	Yes	No
8	Yes	Yes											5	Yes	Yes
9		Yes										Infratemporal	22	Yes	No
10	Yes			Yes					Yes				19	No	Yes (cardiac)
11	Yes												15	No	No
12													21	No	Yes
13	Yes							Yes					-	-	-
14	Yes												-	-	-

It is necessary to mention that among these patients, one patient died due to relapse and complications of MOE and another one died due to cardiac disorder
Abbreviation: JVT Jugular vein thrombosis, CVT Cavernous vein thrombosis, ICA Internal carotid artery, LOS Length of stay, MOE Malignant otitis externa

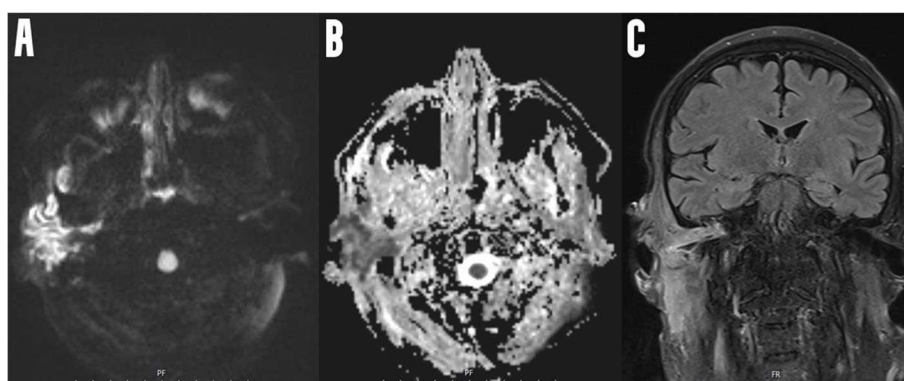


Fig. 1 Diffusion-weighted imaging (DWI) (A) MRI and the corresponding ADC maps (B) revealed restricted diffusion in right ear canal, mastoid and petrotic skull base. Sagittal fluid attenuated inversion recovery (FLAIR) (C) sequences showed marked hyperintensity due to edema extending longitudinally and centrally beyond of ear canal and structures

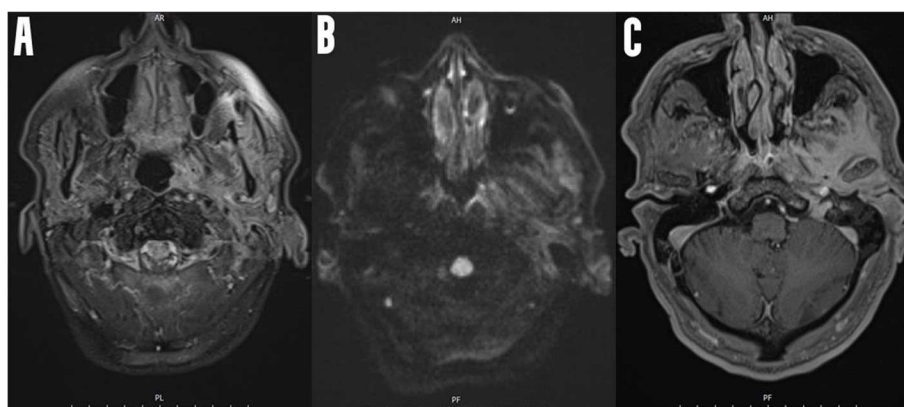


Fig. 2 FLAIR (A), DWI (B) and T1 post-gadolinium (C) sequences revealed diffuse extensive edema and inflammation in the left ear, peri-mandibular joint, deep face spaces and pterygopalatine fossa

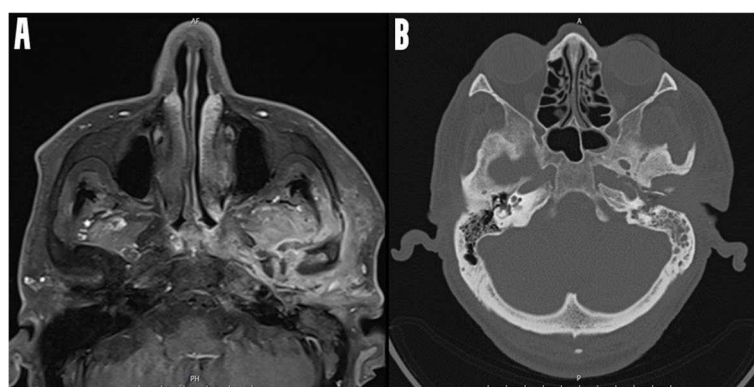


Fig. 3 A Diffuse edema and post-gadolinium enhancement of the left skull base and soft tissue in T1 sequences. B The destructive changes in skull base and petrosal bone, and mastoiditis in computed tomography imaging

Based on the multinomial logistic regression results and analysis of the above-mentioned underlying conditions (DM, HTN, IHD, and renal disease) as covariates,

none of the specific underlying diseases had an association with mortality or relapse of MOE. However, patients with a higher number of underlying diseases were

Table 4 Laboratory findings and their association with relapse of MOE, mortality, and hospitalization. *P*-value < 0.05 is statistically significant

Variables	Descriptive	Relapse (<i>p</i> -value)	Mortality (<i>p</i> -value)	LOS* (<i>p</i> -value)
CBC				
Hb (mg/dl)	11.26 ± 2.00	0.159	0.128	0.03
WBC (10 ³ /μl)	8.73 ± 3.16	0.338	0.456	0.938
Platelet (10 ³ /μl)	230.60 ± 71.52	0.094	0.437	0.952
Inflammatory markers				
ESR (mm/h)	50.54 ± 29.98	0.386	0.015	0.443
CRP (mg/dl)	34.81 ± 25.94	0.049	0.527	0.244
Blood glucose				
FBS (mg/dl)	193.54 ± 101.03	0.991	0.304	0.273
HbA1C (%)	8.94 ± 2.54	0.380	0.729	0.874
Renal Function				
BUN (mg/dl)	25.19 ± 14.09	0.197	0.390	0.213
Cr (mg/dl)	1.68 ± 1.43	0.564	0.137	0.719
BUN/Cr	38.40 ± 86.22	0.158	0.261	0.317

Patients with CN involvement are hospitalized for more than 20 days on average

Abbreviations: LOS length of stay, CBC complete blood count, Hb hemoglobin, WBC white blood cell, ESR erythrocyte sedimentation rate, CRP c-reactive protein, FBS fasting blood sugar, HbA1C hemoglobin A1C, BUN blood urea nitrogen, Cr creatinine

*A cutoff of 20 days is used to analyze LOS

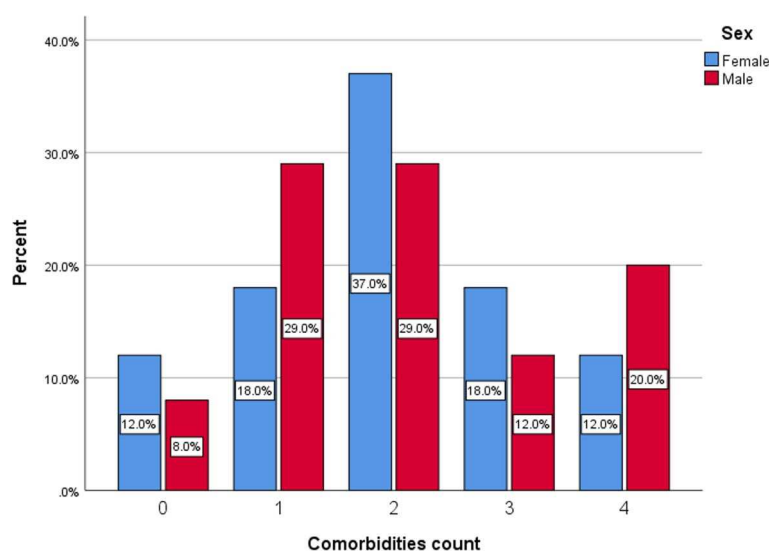


Fig. 4 Cluster bar for most common comorbidities counts in patients based on gender. The Y-axis indicates the relative percentage of legend subgroups

reported to have higher mortality rates and longer LOS (*p*-values = 0.046, 0.019 respectively). Also, as expected, the number of underlying diseases had an association with age, meaning that older patients had more underlying conditions (*p*-value=0.003).

Immune system status

Out of 40 patients, 35 (87.5%) were known cases of poorly controlled diabetes mellitus (DM), two patients

were immunosuppressed due to renal transplant, and one patient had a past medical history of lung cancer. None of the patients were infected by human immunodeficiency virus (HIV). Five cases had more than one risk factor and four cases had none of the above-mentioned risk factors; however, one of these patients was mentally disabled and was unable to express the pain at the beginning of the course of the disease (Table 1).

Complications

As a complication of MOE, in order of prevalence, bone involvement was reported in 22 (55%) according to imaging, chronic otitis media in 18 (45%), cranial nerve involvement in 13 (32.5%), and tympanic involvement in 11 (27.5%) patients.

Our analysis showed no significant association between any of the mentioned complications with mortality and relapse of MOE except cranial nerve involvement that was associated with more than 20 days of hospitalization (p -value = 0.034) (Table 1).

Treatment

Of the 40 included cases, 34 were treated with broad-spectrum antibiotics with activity against gram-positive bacteria. Of these, 25 received vancomycin/clindamycin, 6 received linezolid, and 3 received vancomycin/clindamycin followed by linezolid. Six patients did not receive any antibiotics against gram-positive bacteria. Thirty-nine patients in the study received antibiotics with coverage against *Pseudomonas* species. Twenty-four patients were treated with carbapenems including imipenem, meropenem, and carbapenem, 13 patients were treated with fluoroquinolones including ciprofloxacin and levofloxacin, 12 patients were treated with antipseudomonal cephalosporins including ceftazidime and cefepime, and 3 were treated with piperacillin/tazobactam (Tazocin). Two patients received cephalosporins other than ceftazidime and cefepime (including ceftriaxone), and two patients received penicillins other than piperacillin/tazobactam. Three patients were treated with aminoglycosides including gentamicin and amikacin as an adjuvant therapy.

Patients were divided into "monotherapy" and "dual therapy" groups based on the number of antipseudomonal antibiotics administered. There was no difference in mortality and relapse of the disease between these two groups.

Additionally, there were no differences in mortality and relapse of the disease between patients treated with fluoroquinolones, carbapenems, ceftazidime, or cefepime and those treated with both fluoroquinolones and carbapenems.

Follow-up

Our follow-up duration was $3.52(\pm 3.12)$ years, with a minimum of 1 and maximum of 10 years. During a total of 74 person-years of follow-up, 10 (47.6%) reported persistent symptoms, 6 (16.2%) patients still had otorrhea, five (13.5%) had otalgia, seven (18.9%) had various levels of hearing loss, three (8.1%) had tinnitus, and two (5.4%) had a very mild hemifacial palsy. Six (16.2%) patients experienced a relapse and 11 (29.7%) of all patients died

during the course of MOE. Among these deaths, two were attributed to cardiac events, two cases to kidney failure, one to COVID-19, and one to mucormycosis. The causes of other deaths were not determined during the follow-up calls.

Discussion

MOE is a potential external ear canal infection mostly found in diabetic or immunocompromised patients that invade the cartilage and bones and cause cranial nerve involvement, skull base osteomyelitis, and other life-threatening complications [6, 7, 9]. Of all 40 cases, most were elderly, but some were younger than 40. Consistent with another study [14], MOE was more common in men than women (3:2, $p > 0.05$), most of whom had uncontrolled diabetes. Here we discuss the results and review the literature:

Underlying disorders

Among the patients, it was observed that diabetes mellitus, hypertension, ischemic heart disease, and renal disorders prevailed as the most frequent underlying illnesses. Nevertheless, a mere 10 percent of individuals exhibit no underlying condition, whereas a quarter possess one, and the remaining have more than one disease. Out of the four patients without underlying conditions, one was mentally disabled and unable to express the pain. Further evaluations of these patients yielded no evidence of any presence of DM, HIV, or other primary or secondary immunocompromised statuses. It has been observed that patients who are less than 40 years old had fewer underlying conditions (independent t-test, $p = 0.033$). This finding implies that while MOE primarily affects the elderly population, there are instances where it may also occur in younger individuals. It has shown that individuals harboring a greater number of underlying disorders demonstrate an elevated mortality rate ($P = 0.046$) and an extended hospitalization period exceeding 25 days ($p = 0.04$). However, they failed to reach a significant difference when considering the relapse of MOE ($p = 0.203$). The initial findings regarding FBS and HbA1c levels were not associated with LOS, mortality, or relapse. Prior investigations have suggested that the majority of patients diagnosed with MOE also suffer from diabetes [14–17], except one study which revealed that admissions of diabetic patients constituted merely 22.7% of the total cases explored [12]. A large case-control study has revealed individuals afflicted with diabetes face a significantly elevated susceptibility to the onset of MOE, in contrast to non-diabetic cases with an adjusted odds ratio of 10.07 [15]. On the other hand, some studies confirmed that HbA1c levels were positively correlated with length of stay [18, 19]. Furthermore, it was revealed by Sylvester

MJ et al. that among elderly patients, advancing age was linked to mortality regardless of the presence of diabetes mellitus [12]. However, we indicated that age and diabetic status were not significantly related to mortality, relapse, or LOS. Considering the immune system status, it has come to our attention that a significant majority of patients were in poorly controlled diabetes, two patients had renal transplant history, and one had been diagnosed with cancer. This data serves as an indication that patients having a medical history involving DM, cancer, or transplantation, are prone to experience MOE.

Symptoms/signs and laboratory findings

Otalgia, otorrhea, hearing loss, headaches, and tinnitus were the most reported primary symptoms. Less than half of the patients exhibited symptoms of headaches and tinnitus. Otalgia was also the most common symptom in the literature [18, 20, 21]. Otorrhea and EAC edema were the other frequent symptoms in our patients and were likewise documented in the literature [10, 14]. The laboratory results revealed that the majority of the patients exhibited uncontrolled diabetes (FBS: 193.54 ± 101.03 , HbA1c: 8.94 ± 2.54). It is worth noting, however, that these findings were not statistically significant in regards to mortality or relapse, except for inflammatory markers: elevated ESR levels were associated with higher mortality ($p = 0.015$), while increased CRP levels correlated with a greater risk of relapse ($p = 0.049$). This assertion implies that laboratory tests hold little importance in accurately diagnosing MOE unless they are employed to determine the underlying condition and its severity. According to existing literature, both ESR and CRP serve as valuable parameters for assessing prognosis and monitoring the treatment response [19, 22, 23].

Complications

Facial nerve palsy solely manifests as cranial nerve involvement in a significant proportion of these individuals, specifically recorded at 32.5%. This affliction notably prolongs their stay for more than twenty days (independent t-test, $p = 0.032$). In 2015, Hatch JL et al. showed that facial nerve palsy was positively correlated with LOS [11]. Based on the discerned imaging results, it has been determined that mastoiditis and temporomandibular joint arthritis stand as the prevalent complications stemming from MOE. Nevertheless, these particular consequences have not displayed a significant correlation with death or relapse. The imaging also reveals the potential for bone erosions and osteomyelitis to manifest in patients, most notably affecting the temporal and/or mandible regions. However, it is worth noting that the involvement of the sphenoid and occiput cannot be disregarded. It has been ascertained that the advancement

of age and poor-controlled DM augment the likelihood of osteomyelitis extension beyond the temporal bone. The observed vascular complications encompassed the occurrence of thrombosis within the jugular vein and/or cavernous vein, as well as narrowing of the internal carotid artery alongside manifestations of vasculitis. Meningeal enhancement in MRI showed a probability of meningeal involvement. One patient died during hospitalization at our center probably due to the spread of disease. Eleven patients subsequently died in other studies at other centers. Cardiac events, renal failure, COVID-19 infection, and the development of mucormycosis were the main causes of death. This suggests that although the MOE can be fatal, the underlying disease and its symptoms may be the main cause of death.

In the MOE, facial nerve palsy is the most common cranial nerve disorder, usually occurring in critical illness, with a frequency of approximately 15–50% reported in previous studies [11, 20, 24, 25]. However, one patient was diagnosed with CN VII-XII palsy and the other with collet-sicard syndrome [17, 26]. Exarchos ST et al. first reported a case of CN-XII palsy as the only complication of MOE in 2015 [20]. One study showed that the extent of nasopharyngeal inflammation and facial nerve canal erosion helped the prediction of facial nerve dysfunction. Furthermore, ESR is associated with the involvement of CN VII [27]. In addition to cranial nerve palsy, other important and even life-threatening complications from MOE have also been reported. Zonnour A et al. indicated in 2023 that tinnitus may be a result of skull base osteomyelitis secondary to MOE [25]. Skull base osteomyelitis has been mentioned in the literature as a complication of MOE such as a case report in 2019 or the study conducted by Ferlito S et al. in 2020 [17, 28]. Some other rare complications such as respiratory arrest due to intradural infiltration, vascular complications (internal carotid aneurysm, and maxillary artery pseudoaneurysm), C1/C2 osteomyelitis and atlantoaxial subluxation, Lemierre syndrome, collet-sicard syndrome, and orbital apex syndrome were also reported in the case reports in recent years [26, 29–37].

Diagnoses and differential diagnosis

The patients' diagnoses were determined through a comprehensive evaluation of their clinical presentations, resistance to initial therapy, potential risk factors, and imaging results. Due to its rapid imaging capabilities and wide availability, computed tomography was selected to identify the full extent of the disease, as well as bone and skull base involvement. Mastoiditis was identified in every patient whose CT scan results were assessed. CT scan revealed the presence of bone erosions, edema in the extracapsular area (EAC), and inflammation in the soft

tissues, as well as the temporomandibular joint (TMJ). These findings are not related to the outcome. Additionally, we assessed complications, vascular and meningeal involvement, injuries to the tissue and brain parenchyma, and disease extension, and generally gathered more data from the patients using the MRI modality.

Technetium-99m and MRI were found to be more highly sensitive modalities for diagnosing MOE than temporal CT scans and were also useful for initial diagnosis, disease staging, and complications [22, 28, 38]. Additionally, Positron Emission Tomography-Computed Tomography (PET-CT) is emerging as highly sensitive imaging modality for the diagnosis and management of MOE. It is particularly useful for assessing the extent of the disease and monitoring the treatment response [39]. EAC edema and irregularities have been reported as early findings on CT scans [40]. Bone erosions and soft tissue involvement have been also mentioned in a meta-analysis [38]. In general, CT scan and MRI are two preferred modalities for diagnosing MOE among physicians. Nuclear medicine imaging is becoming less common, even though it is essential for osteoblastic activity during the disease's remission phase [28, 41]. One study mentioned that ADC signal findings on diffusion-weighted MRI may help decide whether to discontinue or continue treatment [42]. Adenocarcinoma metastases in the temporal bone and nasopharyngeal carcinoma are important differential diagnoses of MOE that have been mentioned in case reports [43, 44]. These suggest that, within the context of risk factors, it is important to evaluate metastases and malignancies as differential diagnoses of MOE. Peled C et al. in 2021 found that TMJ involvement mostly occurs with fungal pathology and it is recommended to initiate the administration of antifungal drugs in the cases of TMJ involvement and sterile culture MOE [45]. Additionally, despite its rarity, fungal MOE can lead to severe complications, including cranial nerve involvement, as well as intracranial and cerebrovascular complications [46].

Management

All patients were administered systemic and topical antibiotics (e.g. ciprofloxacin) in addition to topical corticosteroids. They then recovered, were discharged, and continued their medical therapies for 4–8 weeks, while one patient died in the hospital, possibly due to the progression of life-threatening complications. This suggests that the treatment of MOE is challenging and requires long-term monitoring. Based on the results observed during hospitalization, our study concluded that the recommended antibiotic regimens are effective. The main purpose of our antibiotic selection was to cover

P. aeruginosa and gram-positive bacteria. To achieve this, we selected potent antibiotics active against gram-positive bacteria, including vancomycin, clindamycin, and/or linezolid. Additionally, we recommended antipseudomonal therapy with ceftazidime, cefepime, and piperacillin/tazobactam. In addition, aminoglycosides were selected as adjuvant therapy. In addition to medical therapy, 9 (22.5%) patients received surgical therapy (debridement and radical mastoidectomy), which was not significantly associated with mortality, relapse, or LOS. The operation rates in the two studies were 19.2% and 24%. Despite our results, one study showed that surgical procedures were significantly associated with older patients, longer length of stay, and relapse of MOE. Moreover, early surgery prevents the development of complications [11, 47, 48].

High-resolution CT (HRCT) findings of the temporal bone such as extensive bony erosion, involvement of the skull base, and presence of soft tissue density extending external auditory canal, treatment resistance, and fungal infection indicate the need for surgical therapy [21, 49]. Treatment resistance is defined by persistent infection despite appropriate medical therapy. Cases that show no clinical improvement or worsening symptoms after an adequate trial of antibiotics may be classified as treatment-resistant [49]. Fungal infections, particularly those caused by *Candida* and *Aspergillus* species, can complicate MOE. Surgical intervention may be necessary in these cases to remove necrotic tissue and control the infection, as medical therapy alone may not be sufficient [50].

Antibiotic therapy is a pivotal treatment in the management of MOE and requires long-term therapy [51, 52]. Treatment requires 6–8 weeks of antibiotics as a study showed that 2 weeks of piperacillin-tazobactam followed by 6 weeks of ciprofloxacin leads to better outcomes. Complicated patients with cranial nerve palsy or bone erosion require long-term individualized therapy and follow-up [51, 53–55]. Ceftazidime monotherapy seems to be useful, while another study recommends culture-based dual therapy to prevent treatment failure and antimicrobial resistance [51, 55]. Culture-based selection of antibiotics is critical for better management of MOE and prevention of antimicrobial resistance [56–59]. It is recommended to start antifungal medications early to prevent the spread of infection and cranial nerve dysfunction [52]. Ideally, antifungal treatment should be started as soon as fungal infection is suspected or confirmed, even before culture results are available [60]. The choice of antifungal depends on the specific fungal pathogen. Commonly used antifungals include azoles (e.g., fluconazole, itraconazole, voriconazole) and polyenes (e.g., amphotericin B). For example, voriconazole is often

used for *Aspergillus* infections, while fluconazole is used for *Candida* species [61]. Early use of antifungal treatment helps to prevent the spread of infection to adjacent structures, including cranial nerves, which reduces the risk of cranial nerve dysfunction [62]. Hyperbaric oxygen therapy is a well-tolerated, beneficial adjuvant therapy that may reduce complications, mortality, and hospitalizations, and is useful in the treatment of MOE [63, 64]. This treatment can be indicated in extensive soft tissue involvement and bone erosion despite appropriate antibiotic therapy, diabetic and immunocompromised patients to enhance the healing, and persistent symptoms despite appropriate medical therapy [65]. Control of the underlying disease, especially diabetes mellitus, early diagnosis of patients with clinical findings, and close monitoring of patients, especially complicated patients with increased ESR, CRP, symptom/signs, and imaging, can prevent the progression of life-threatening complications and give rise to better management [58, 66].

Limitations

The small sample size was the most important limitation of our study. Although we collected the information from a tertiary center, the sample size is small due to the rarity of MOE. Therefore, it is necessary to conduct multicenter studies to collect more cases and improve the generalizability of the results to other populations and settings. Another limitation of this study is that it is retrospective. Further prospective studies are required to confirm and/or complement our results. Despite these limitations, the study provides useful insights into the clinical features, diagnosis, and management of MOE.

Conclusions

Based on our results, we concluded that MOE is a potential disease that requires early diagnosis and treatment to prevent the spread and development of complications. It can occur especially in poorly controlled diabetics and patients with cancer or organ transplants. However, some patients may have no known predisposing factors despite a comprehensive evaluation. Clinical findings, risk factors, resistance to therapy, and radiological findings can be used for early detection of the disease. CT scan and MRI are two practical modalities for early diagnosis of MOE and assessment of complications. In case of complications, extension of osteomyelitis beyond the temporal bone may occur in elderly patients and poorly controlled DM. Finally, coverage of Gram-positive and *P. aeruginosa* is an effective strategy for treating MOE, relieving symptoms and complications, and improving patient outcomes.

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Clinical trial

Not applicable.

Authors' contributions

Contributions Arefeh Tabashiri: Data extraction, patient follow-up, manuscript draft, data analysis fHadi Allahverdi Nazhand: Data extraction, patient follow-up, manuscript draft, data analysis Mobin Fathy: Data extraction, patient follow-up Seyed Mohammad Mortazavi: Data extraction, patient follow-up Farid Javandoust Gharehbagh: Language editing fMaryam Haghighi-Morad: Re-examination of radiological documents Farhad Mokhtarinnejad: ENT counseling Ilad Alavi Darazam: Study concept and design, critical revision of the manuscript for important intellectual content, study supervision.

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Data availability

All data are available within the manuscript.

Declarations

Ethics approval and consent to participate

Our study was approved by the Research Ethical Committee of Shahid Beheshti University of Medical Sciences (IR.SBMU.RETECH.REC.1402.211), in accordance with the Declaration of Helsinki [67].

Considering the nature of the study, informed consent was deemed unnecessary according to international regulations. Our research focused on analyzing existing data. The ethics committee approved the waiver of informed consent because the study could not be practically conducted without it, and it did not negatively impact the rights and welfare of the participants. All data were anonymized to ensure confidentiality and privacy.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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