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Malignant Otitis Externa: An Experience of A 27-Year Period

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ABSTRACT

Background and Aim: Malignant otitis externa is a rare but potentially fatal infection. It tends to affect the elderly as well as patients with diabetes and immunocompromised status. We aimed to identify the epidemiological, clinical, therapeutic, and evolutionary features of malignant otitis externa.

Materials and Methods: We conducted a retrospective study including patients hospitalized in the infectious diseases department in Sfax (South of Tunisia) for malignant otitis externa between 1994 and 2020. Non-documented cases were excluded from the study at enrolment.

Results: We encountered 82 patients, among whom 45 were male (54.9%). The mean age was 62 ±14 years. Seventy-four patients had diabetes mellitus (90.2%). The most common clinical symptoms were otalgia (86.5%) and otorrhea (69.5%). *Pseudomonas aeruginosa* was the most common organism (56%). The first-line antimicrobial used on admission was a combination of ciprofloxacin (65.8%) and ceftazidime (51.2%). The median duration of treatment was 6 weeks [4-32 weeks]. The disease evolution was favorable in 67 cases (81.8%). According to the length of hospital stay, patients hospitalized for ≥ 21 days consulted after significantly longer duration of complaints (49 days vs. 36 days; *P*=0.01) and had significantly more frequent complications (35.3% vs. 10.4%; *P*<0.001), while the recovery was significantly more frequent in patients hospitalized less than 21 days (89.6% vs. 70.6%; *P*=0.02).

Conclusion: Despite advancements in treatment and the variability of imaging modalities, malignant otitis externa remains a fatal disease. The diagnostic delay may worsen the disease outcome, requiring a longer duration of treatment and referral to surgery.

Keywords: Computed tomography scan, Magnetic resonance imaging, Malignant otitis externa, Prognosis, *Pseudomonas aeruginosa*

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1 Introduction

Malignant otitis externa (MOE), also known as necrotizing otitis externa, is a rare but potentially fatal infection. The disease usually originates from the soft tissue of the external auditory canal (EAC) and spreads across surrounding structures, resulting in abscesses, cranial nerve deficit, and even death **(1,2)**. The disease-specific mortality rate ranges from 2.2% to 18.8% **(3)**. It tends to affect the elderly as well as patients with diabetes and immunocompromised status **(4,5)**. Patients usually complain of persistent otalgia, purulent otorrhea, headache, and hearing loss **(1)**. Imaging findings help through the diagnostic process when showing local tissue swelling and extensive diffuse bone destruction **(6)**. The

appropriate imaging choice is based on many factors, including its availability, the imaging modality's diagnostic strength, and the clinician's level of suspicion for the diagnosis **(7)**. *Pseudomonas aeruginosa* (*P. aeruginosa*) is the most common pathogen incriminated **(8)**. *Staphylococcus aureus*, *Klebsiella* species, and fungal pathogens were reported **(9)**. As soon as the diagnosis is established, prolonged antimicrobial therapy is indicated with referral to surgical debridement, occasionally **(10)**.

In our region, recent and exhaustive data about MOE are lacking. Studying its clinical particularities would help physicians shorten the diagnosis delay and improve its management. In this perspective, the aim of this work was to identify the epidemiological, clinical, therapeutic and evolutionary features of MOE.

2.Materials and Methods

Study Design

We conducted a retrospective study including all patients hospitalized in the infectious diseases department in Sfax (South of Tunisia) for MOE between 1994 and 2020.

Inclusion Criteria And Data Collection

Data were collected from the patient's records on pre-established sheets. We collected socio-demographic characteristics such as age, gender, comorbidities, and urbanity of residence. Clinical data such as the presenting signs, the physical examination result, the otoscopic examination results, laboratory data, and the causative organism were noted. Therapeutic and evolutionary data were noted by specifying the treatment modality, the antibiotics or the antifungal therapy received, and its duration.

The disease evolution was defined as favorable when patients showed improvement regarding the reduction of pain and decrease in ear discharge under treatment with the disappearance of the initial abnormalities found on otoscopic examination. The absence of relapse after stopping the treatment confirms the favorable evolution of the disease.

The diagnosis of MOE was confirmed with **(1)**:

- Compatible physical examination of severe otalgia, external ear canal edema, exudate, and granulations.
- Failure to respond to systemic and local antibiotic treatment for at least 10 days.
- Positive finding on imaging results.
- The growth of bacterial and/or fungal species in the ear sample.

All cases of non-documented MOE were excluded from the study at enrolment.

We divided patients in two groups according to the duration of hospitalization: group A represented patients hospitalized less than 21 days and group B represented patients hospitalized longer than 21 days.

Statistical Analysis

All statistical analysis was performed using the SPSS 20 software. Categorical variables were expressed as numbers and percentages, while continuous variables were expressed by means and standard deviations if they were normally distributed. Otherwise, medians and interquartile ranges were performed. We used the Chi-square test to compare two frequencies and the Student test to compare two means in independent samples. We considered the difference between the groups significant when P-value<0.05.

3.Results

Patients' Characteristics

Over a 27-year period, we encountered 82 patients with MOE, among whom 45 were male (54.9%). The mean age was 62 ±14 years. According to the urbanity of residence, 58 patients came from urban areas (70.7%). Seventy-four patients had diabetes mellitus (90.2%), among whom 36 cases required insulin injections (43.9%). A total of 23 patients had associated hypertension (28%), and 5 patients had a chronic renal failure (6%). Eighteen patients experienced a previous episode of otitis externa (21.9%) (Table 1).

Table 1. Patients' characteristics, clinical presentation, physical examination results and the disease evolution

Variables		Number	Percentage (%)
Total		**82**	**100**
Gender	Males	45	54.9
	Females	37	45.1
Age groups (years)	<50	13	15.9
	50-64	26	31.7

	65-74	26	31.7
	≥75	17	20.7
Co-morbidities	Diabetes mellitus	74	90.2
	Hypertension	23	28
	Chronic renal failure	5	6
	Immunosuppressive medication	4	4.8
	Hematological malignancy	2	2.4
	Solid tumor	2	2.4
Complaints	Otalgia	71	86.5
	Otorrhea	57	69.5
	Cephalalgia	36	43.9
	Hearing loss	28	34.1
	Tinnitus	18	21.9
	Fever	16	19.5
	Vertigo	11	13.4
	Otorrhagia	8	9.7
Physical examination findings	Mastoid bone tenderness	39	47.5
	Painful tragus	37	45.1
	TMJ tenderness	24	29.3
	Peripheral facial nerve palsy	11	13.4
	Cervical lymphadenopathy	8	9.7
Otoscopic examination results	Stenosis of the EAC	65	79.2
	Inflammation of the EAC	48	58.5
	Polyp	22	26.8
	Granulation tissue in the EAC	17	20.7
Disease evolution	Favourable	67	81.8
	Relapse	9	11
	Sequelae	2	2.4
	Death	4	4.8

EAC: external auditory canal; TMJ: temporomandibular joint

Before admission, the number of previous consultations varied from 1 to 8 consultations for persistent symptoms. At presentation, otalgia was the most common clinical symptom, noted in 71 cases (86.5%) and followed by otorrhea in 57 cases (69.5%). Physical examination revealed, besides otorrhea (69.5%), tenderness to palpation of the mastoid bone (39 cases; 47.5%) and pain upon palpation of the tragus (37 cases; 45.1%). Tenderness to palpation of the temporomandibular joint was noted in 24 cases (29.3%). Otoscopic examination results included stenosis and inflammation of the EAC in 65 cases (79.2%) and 48 cases (58.5%), respectively (Table 1). Inflammatory markers revealed an elevated C-reactive protein level (CRP) in 53 cases (64.6%) and leukocytosis with a neutrophil predominance in 18 cases (21.9%). Other laboratory investigations showed hyperglycemia with a mean glucose level of 12 ± 5 mmol/L.

P. aeruginosa was the most common organism isolated in 46 cases (56%). It represented 79.3% of the bacterial MOE cases (58 cases). Depending on their antimicrobial sensitivity profiles, *P. aeruginosa* isolates were susceptible to ceftazidime and gentamicin in 82% and 67.3%, respectively. Each was susceptible to imipenem and ciprofloxacin in 40 cases (86.9%). Fungal species were isolated in 37 cases

(45.1%), represented mainly by *Candida species* in 24 cases (29.3%), and followed by *Aspergillus species* in 13 cases (15.9%). In total, MOE was caused by mixed bacterial and fungal infection in 13 cases (15.9%) (Table 2). Both *Aspergillus* serology and antigenemia were positive in 9 cases (69.2%). As for *Candida* infection, serological tests were positive in 15 cases (62.5%).

Table 2. Causative microorganisms isolated from patients with malignant otitis externa

Causative microorganisms	Number	Percentage (%)
Bacterial infection	58	70.7
Pseudomonas aeruginosa	46	56
Klebsiella pneumoniae	3	3.6
Coagulase-negative staphylococci	3	3.6
Escherichia coli	2	2.4
Corynebacterium	2	2.4
Proteus mirabilis	2	2.4
Fungal species	37	45.1
«*Candida* species»	24	29.3
Candida parapsilosis	15	18.2
Candida albicans	7	8.5
Candida krusei	1	1.2
Candida tropicalis	1	1.2
«*Aspergillus* species»	13	15.9
Aspergillus flavus	7	8.5
Aspergillus sp	3	3.6
Aspergillus fumigatus	1	1.2
Aspergillus niger	1	1.2
Aspergillus terreus	1	1.2
Mixed bacterial and fungal infection	13	15.9

In order to exclude possible malignancy and to confirm our diagnosis, biopsies of the EAC were performed in 16 cases (19.5%), and the histopathology examination results showed extensive inflammation in all cases associated with filamentous fungus in 2 cases (2.4%).

Computed tomography (CT) scan of the temporal bone showed stenosis of the EAC in all cases, suggestive bone erosion in 56% of the cases, and mastoiditis in 47.5% of the cases (Figure 1).

Osteomyelitis was noted in 5 cases (6%). Magnetic resonance imaging (MRI), performed in 12 cases (14.6%), confirmed the results found on the CT scan (Figure 2). Technetium scintigraphy was performed in 20 cases (24.3%) and showed increased activity in the temporal bone and/or the skull bases bone in all cases.

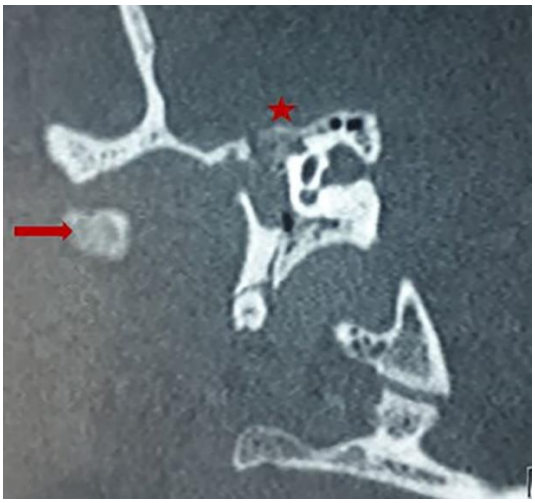

Figure. 1. Coronal section of a computed tomography scan demonstrating osteolysis of the right tympanic bone (*) and lysis of the homolateral mandibular condyle (arrow)

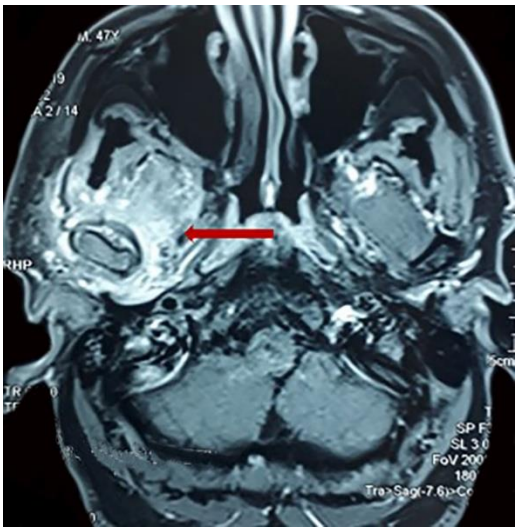

Figure. 2. Axial magnetic resonance imaging FLAIR after gadolinium injection showing abnormal soft tissue of the right skull base with heterogeneity in the parapharyngeal space and the infra-temporal fossa (arrow)

The most common first-line antimicrobial used on admission was a combination of ciprofloxacin (65.8%) and ceftazidime (51.2%). Imipenem was used in 28% of the cases. In total, 21 patients received fluconazole (25.6%), and 13 patients received voriconazole (15.9%). The median duration of treatment was 6 weeks [4-32 weeks]. Two patients (2.4%) underwent surgery (debridement). Two patients (2.4%) received supplementary treatment with hyperbaric oxygen therapy in front of the worsening clinical and radiological findings despite adequate therapy.

The disease evolution was favorable in 67 cases (81.8%). The mean duration of hospital stay was 24 ± 17 days. Complications were noted in 17 cases (20.7%) represented by the appearance of contralateral otitis (53%) and skull base osteomyelitis (29.4%). We noted 3 cases (17.6%) of cerebral venous thrombosis. Relapse was noted in 9 cases (11%) and sequelae in 2 cases (2.4%). Four patients were dead (4.8%) (Table 1).

Comparison of Patients According to the Length Of Hospital Stays

We compared 48 cases of MOE (58.5%) that required hospitalization for less than 21 days (group A) with 34 cases (41.5%) that required hospitalization for ≥ 21 days (group B). The duration of complaints before hospitalization was significantly longer among group B (49 days vs. 36 days; *P*=0.01). Otalgia and otorrhea were the most common complaints among both groups. Peripheral facial nerve palsy was significantly more frequent in group B (26.5% vs. 4.2%; *P*=0.005). Painful tragus (58.8% vs. 35.4%; *P*=0.03), granulation tissue (35.3% vs. 10.4%; *P*=0.006) and polyp in the EAC (44.1% vs. 14.6%; *P*=0.003) were significantly more frequent among group B. The left ear was significantly more affected among group A (60.4% vs. 32.3%; *P*=0.01). A comparison of the disease evolution showed that complications were significantly more frequent among group B (35.3% vs. 10.4%; *P* < 0.001), while the recovery was significantly more frequent among group A (89.6% vs. 70.6%; *P*= 0.02). There were four cases of death in group B (11.8%) (Table 3).

Table 3. Comparison of patients based on the duration of hospitalization

	Groupe A (L < 21 days)	Groupe B (L ≥ 21 days)	P-value
Total, n (%)	48 (58.5%)	34 (41.5%)	-
Mean age ± SD (years)	61 ± 15	65 ± 10	0.4
Sex (male), n (%)	27 (56.3%)	18 (52.9%)	0.7
Duration of Complaints (days)	36	49	0.01
Affected ear (left ear), n (%)	29 (60.4%)	11 (32.3%)	0.01
Complaints, n (%)			
Otalgia	42 (87.5%)	29 (85.3%)	0.5
Otorrhea	33 (68.8%)	24 (70.6%)	0.8
Peripheral facial nerve palsy	2 (4.2%)	9 (26.5%)	0.005
Physical examination findings, n (%)			
Painful tragus	17 (35.4%)	20 (58.8%)	0.03
Mastoid bone tenderness	22 (45.8%)	17 (50%)	0.7
Polyp	7 (14.6%)	15 (44.1%)	0.003

	Groupe A (L < 21 days)	Groupe B (L ≥ 21 days)	P-value
Granulation tissue	5 (10.4%)	12 (35.3%)	0.006
Disease evolution, n (%)			
Favorable	43 (89.6%)	24 (70.6%)	0.02
Complications	5 (10.4%)	12 (35.3%)	0.006
Relapse	6 (12.5%)	3 (8.8%)	0.4

L: length of hospital stay, n: number, %: percentage, SD: standard deviation

4.Discussion

Our study highlighted the substantial burden of MOE, especially among the elderly and diabetic patients. A comparison of the disease evolution showed that the diagnostic delay was associated with a longer duration of hospitalization and the occurrence of complications. Although it has become a treatable disease with new antibiotics, MOE is a potentially devastating condition with a poor outcome during severe cases **(1)**. In fact, the diagnostic delay is correlated to the development of a complication. This delay might be explained by the lack of a consensus regarding diagnostic criteria **(11)**. Some authors have reported 3 parameters for the diagnosis of MOE, including clinical findings such as polypoidal granulation tissue arising from the EAC, raised serum inflammatory markers, and radiographic evidence of soft tissue, with or without bone erosion, in the EAC and infratemporal fossa **(12,13)**. However, the most common criteria used by most clinicians are the presence of granulations, otalgia, edema, otorrhea, and resistance to local treatment for at least 8 to 10 days **(1)**. The occasional criteria, which alone do not confirm the diagnosis, include diabetes, cranial nerve involvement, positive radiograph, debilitation condition, and old age **(1,12)**.

Previous studies showed that MOE was associated with aging and comorbidities, especially diabetes and immunodeficiency disorders **(14)**. Increasing age significantly impacts disease incidence and mortality **(15)**. However, patients with human immunodeficiency virus infection who develop MOE tend to be younger than the typical patient, and most of them do not have diabetes **(13)**. In fact, the link between advanced age and MOE might be explained by the decreased epithelial migration of the ear canal and microvascular disease inhibiting a proper immune response **(15)**. Diabetes is also associated with impaired immune response and microvascular disease, which explains MOE frequency among diabetic patients **(15)**. In our study, diabetes was observed in 90.2% of the cases.

The most common revealing symptoms were otalgia, otorrhea, and temporal headaches **(4,16)**. Otorrhea was often the earliest symptom, with headaches occurring after 2 weeks to 6 months **(16)**. As the disease progresses, patients can rarely present with cranial nerve involvement, which indicates a poor prognosis **(17,18)**. MOE diagnosis should be suspected in front of persistent clinical symptoms, in a diabetic or immunocompromised patient, especially in cases of resistance to local and symptomatic treatment. Otoscopic examination usually reveals features of MOE, such as the presence of EAC discharge, edema, and granulations **(4)**.

Imaging findings play a role during the diagnostic process. However, no radiological investigation provides sufficient detail to diagnose MOE and monitor treatment **(12)**. Both CT-scan and MRI provide excellent resolution of soft tissue infection in the subtemporal region and the stylomastoid foramen **(19)**. CT is sensitive to bone erosion and is of particular value in assessing the middle ear, mastoid, bony facial nerve canal, petrous apex, and carotid canal. However, at an early stage of osteomyelitis, bony changes may not be evident on a CT scan **(19)**. At that stage, MRI is superior since it detects bone marrow edema, which precedes the cortical bone erosion **(20)**. In our study, the CT scan was performed in all cases, while MRI was performed in 14.6% of the cases. Besides, nuclear medicine has traditionally been used for the initial diagnosis of osteomyelitis by identifying sites of increased osteoblast activity. However, it is unable to differentiate between active infection and bone remodeling **(20)**. Nuclear imaging using Technetium-99 is usually helpful for establishing the diagnosis and Gallium-67/Indium-111 labeled leukocyte scintigraphy combined with single positron emission computed tomography (SPECT) helps monitor the disease **(8,21)**. In the light of the variety of radiological examinations, a CT scan is usually performed as the first line of investigation, and the MRI is reserved for patients with suspected intracranial involvement or those with a diagnostic problem **(12,19)**.

The most common offending pathogen is *P. aeruginosa,* reaching 76% of the cases, although it is

not a member of the normal flora of the external ear **(9)**. In our study, it represented 56% of all the cases and 79.3% of the bacterial MOE. *P. aeruginosa* infiltrates blood vessels, causing vasculitis and thrombosis, leading to tissue necrosis. The use of hearing aids, a humid and moist environment, and minor trauma to the ear canal can act as a trigger for this pathogenic process **(10)**. Its rate has been declining in recent years, while rates of sterile MOE have been increasing **(9)**. As for fungal MOE, *Aspergillus spp* and *Candida albicans* are the most implicated fungi. *Candida glabrata* and *Candida parapsilosis* have also been reported **(22)**. In our study, *Aspergillus flavus* and *Candida parapsilosis* were the most common fungal species isolated in 8.5% and 18.2% of the cases, respectively. The diagnosis of fungal MOE might be facilitated with *Aspergillus/Candida* serology and antigenemia.

Known for its excellent penetration into bone, fluoroquinolone, usually ciprofloxacin, or an antipseudomonal cephalosporin such as ceftazidime are prescribed once culture specimens have been taken **(12)**. In order to avoid the development of resistance, treatment should be directed specifically against the agent of the disease **(23)**. However, the result of previous antibiotic intake and sterile MOE may present a diagnostic and treatment challenge. Prolonged treatment for 6 to 8 weeks is generally recommended **(24)**. This period of therapy is based on the time needed for the bone to revascularize **(11)**. However, in our study, recovery required a longer duration of antimicrobial therapy, which is explained by the advanced disease, the severity of cases when the diagnosis was made, and the non-immediate response to treatment. Previous studies reported the need to switch to empirical antifungal treatment for cases of suspected MOE resistant to antibacterial regimens after 7 to 10 days in order to reduce mortality and morbidity **(25)**. Besides medical treatment, referral to surgery was indicated for patients who did not respond to conservative systemic treatment. In the lack of clear guidelines, surgery has been reported in the following circumstances: 1- for debridement of necrotic tissue. 2- when obtaining deep tissue biopsies, especially in culture-negative patients. 3- for surgical exploration in refractory cases. 4- for facial nerve decompression in the presence of facial palsy **(9,26)**. In the case of widespread soft-tissue involvement, surgery with hyperbaric oxygen therapy was associated with a better prognosis, fewer neurologic sequelae, and a lower mortality rate **(27)**.

Previous research recommends observing both CRP and erythrocyte sedimentation rates during the follow-up **(11,28)**. In fact, the erythrocyte sedimentation rate starts to decrease within two weeks of treatment **(29)**. Serial monitoring demonstrated a progressive downward trend in patients who responded quickly to therapy, while a slower decline towards normality was noted in those with extensive skull base disease **(11)**. Even imaging findings, MRI, CT scan, and technetium scintigraphy, are limited in determining the disease resolution as bone changes persist after disease resolution **(19,20)**. Some authors recommend a CT scan or MRI at least 3 months after initiating the treatment to evaluate response, as earlier imaging does not usually show much change **(19)**. Lower cranial neuropathies have been shown to lead to worse outcomes and higher mortality rates **(15)**. The advanced presentation might explain this and the severity of the case correlated to cranial nerve involvement, which typically indicates a progression of the disease. A recent study reported a mortality rate of 7% directly attributed to MOE **(30)**, while in our study, 4.8% of patients were dead. Relapse has been reported to be around 15% to 20%, that's why at least 6 months of follow-up for MOE is ideal **(20)**. In our study, the relapse was 11%.

5.Conclusions

Despite advancements in treatment and the variability of imaging modalities, MOE remains a fatal, highly variable, severe disease occurring mainly among elderly diabetic and immunocompromised patients. The diagnostic delay may worsen the disease outcome, requiring a longer duration of treatment and referral to surgery.

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Conflict of Interest

The authors declare no conflict of interest.

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