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Original Article

A Different Era for Malignant Otitis Externa: The Non-Diabetic and Non-Immunocompromised Patients

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BACKGROUND: To investigate the differences in regard to the clinical, laboratory, and imaging findings as well as the treatment course between diabetic and non-diabetic, non-immunocompromised patients with malignant otitis externa.

METHODS: A total of 36 hospitalized patients diagnosed with malignant otitis externa between January 2011 and December 2020 were divided into 2 groups according to their medical history, blood glucose, and glycated hemoglobin levels.

RESULTS: Thirty-two patients were diabetic (group A) and 4 were non-diabetic, non-immunocompromised (group B). Otalgia was present in all patients (100%), followed by otorrhoea (67%) and edema (64%). Polyps were present in 18 patients (50%). *Pseudomonas aeruginosa* was isolated in 16 out of 25 positive cultures (64%). Four patients of group A and none of group B underwent surgery. Five patients of group A and none of group B had at least 1 cranial nerve involvement. The mean age was 77.22 ± 8.17 for group A and 47.25 ± 3.59 for group B ($P < .001$). No statistical significance was observed in regards to major symptoms, inflammatory markers (white blood cell, C-reactive protein, and erythrocyte sedimentation rate), positive imaging, and microbiological findings between the 2 groups. The average days of hospitalization were 42.41 ± 31.06 for group A and 10.25 ± 2.63 for group B ($P < .049$). Four diabetic patients died.

CONCLUSION: Non-diabetic, non-immunocompromised adult patients with malignant otitis externa had a better response to antibiotic therapy and a shorter length of hospitalization. A high clinical suspicion for malignant otitis externa should always raise in cases of otitis externa that fail to respond in a topic and/or oral antibiotic treatment for more than a week.

KEYWORDS: Cranial nerve palsy, diabetes mellitus, malignant otitis externa, Pseudomonas aeruginosa

INTRODUCTION

Malignant otitis externa (MOE) is a well-recognized and life-threatening form of otitis externa that was named "malignant" by Chandler[1] due to its high mortality. This rare infection of the external auditory canal may subsequently spread to adjacent structures such as the temporal bone and skull base through the fissures of Santorini and typically is caused by *Pseudomonas aeruginosa* in 90% of cases and also by other pathogens.[2,3] It was the classic paper of Cohen and Friedman[4] described the major and minor diagnostic criteria of MOE. Major criteria include otalgia, otorrhea, edema, granulation tissue, positive Tc-99m scan, and microabscess. Minor criteria include *P. aeruginosa* isolation, positive radiograph, diabetes mellitus (DM), old age, cranial nerve involvement, and debilitating condition. Malignant otitis externa typically occurs in patients with DM and immunocompromised patients. Several authors report that the pathogenesis of MOE is related to microangiopathy, hypoperfusion, and diminished host resistance due to DM.[5,6]

However, in the last decade, a growing number of non-diabetic and non-immunocompromised patients suffering from the disease has emerged. The aim of the present study is to investigate the differences in regard to the clinical, laboratory, and imaging findings as well as the treatment and management course between diabetic and non-diabetic, non-immunocompromised patients with MOE.

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METHODS

This study was approved by the Institutional Review Board (IRB) and the Ethics Committee of Attikon University Hospital (number of approval IRB 205/05-04-2021). All patients diagnosed with MOE between January 2011 and December 2020 received informed consent forms according to the institutional guidelines.

The diagnosis of MOE was established by both clinical and imaging findings, according to the major (obligatory) and minor (occasional) diagnostic criteria described by the study of Cohen and Friedman. Malignant otitis externa was diagnosed if all the major criteria were present.

The data analyzed included sex, age, comorbidities, cranial nerve involvement using House Brackmann (HB) score for facial nerve grading, days of hospitalization, and also the values of critical lab tests: blood glucose and glycated hemoglobin (HbA1c) levels, white blood cell (WBC) count, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR). The imaging techniques that have been used include high-resolution computed tomography (HRCT), magnetic resonance imaging (MRI), technetium-99 m (Tc-99m) medronate bone scanning, and gallium citrate Gallium-67 (Ga-67) scintigraphy.

Patients were divided into 2 groups, diabetic and non-diabetic and non-immunocompromised according to their medical history. Daily microscopic examination and cleaning of the external auditory canal were performed in all patients. Cultures were collected from all patients; moreover, a biopsy was done for those with granuloma in the external auditory canal. All patients received intravenous and topical antibiotic treatment (ciprofloxacin) which was modified according to their histologic findings and swab culture results. All patients received oral antibiotic therapy for at least 6 weeks after hospital discharge.

The parameters are described using mean and standard deviation. Analysis of variance test was used to determine the significance of each independent variable. The predictive accuracy was expressed with the 95% CIs. The level of significance was $P < .05$. Statistical analysis was performed using IBM Statistical Package for the Social Sciences Statistics, v. 19 (IBM SPSS Corp.; Armonk, NY, USA).

RESULTS

A total of 36 patients were included in this study; 32 were diabetic (group A) and 4 were non-diabetic (group B).

Twenty-seven of the patients were males and 9 of them were females (26 and 1: group A and 6 and 3: group B, respectively). The mean age was 73.89 ± 12.31 (CI: 74.27-80.16), 77.22 ± 8.17 for group A and 47.25 ± 3.59 for group B ($P < .001$). Severe night otalgia was present in all patients (36/36), followed by otorrhoea (24/36) and edema of the external auditory canal (23/36). Polyps were present in 18 patients (50%).

The total average duration of hospitalization was 38.83 ± 30.99 days (CI: 28.35-49.32), 42.41 ± 31.06 for the DM group, and 10.25 ± 2.63 for the non-diabetic group ($P < .049$).

The mean total WBC count was 8124 ± 1601×10^3/μL (CI: 7582-8665), the mean CRP level was 39.34 ± 25.38 mg/L (CI: 30.76-47.93), and the mean ESR level was 70.19 ± 30.12 mm/h (CI: 60-80.39) at the first examination with no statistical significance between the 2 groups. The mean blood glucose level was 181.5 ± 62.6 mg/dL (CI: 160-203), and the mean HbA1c level was 7.6 ± 1.9% (CI: 7-8.3) with statistical significance between the 2 groups ($P = .001$ and $P = .003$, respectively) (Table 1).

An HRCT scan was performed in all patients. In addition, an MRI scan was performed in 6 patients, a bone scanning using Tc-99m was performed in 16 patients, and a scintigraphy using Ga-67 was performed in 20 patients. Positive imaging findings were present in 30 of 36 HRCT scans (83%), 5 of 6 MRI scans (83%), 22 of 26 Tc 99 bone scans (85%), and 12 of 16 Ga-67 scintigraphy (75%).

Group A: Surgical intervention was performed in 4 patients and a ventilation tube was placed in 5 patients. Five patients (14%) had at least 1 cranial nerve involvement. All of them had facial nerve paralysis (3 patients with HB grade III, 1 with HB grade IV, 1 with HB grade VI), 2 of them (6%) had glossopharyngeal and 1 patient (3%) had vagus nerve involvement.

Group B: All 4 patients had otalgia, otorrhea, swollen external auditory ear canal, and positive Tc 99 findings. None of them had cranial nerve involvement. The mean duration of symptoms before diagnosis was 14 days. Two of them had polyps in the external ear canal. A ventilation tube was used in 1 patient (Table 2).

A total of 25 positive out of 36 cultures were identified. In 17 cultures, a single pathogen was identified. The remaining 8 revealed polymicrobial infection. *P. aeruginosa* was present in 16 patients (64%), *Staphylococcus* species in 7 patients (19%), *Streptococcus* species in 2 patients (6%), *Candida albicans* in 2 patients (6%), and others (*Alternaria spp, Bacillus spp, Enterobacter, Acinetobacter baumanii,* and *Finegoldia magna*) in 5 patients (14%). As regards the survival rates, 32 patients completed the long-term treatment successfully and 4 of them died (group A patients).

DISCUSSION

Several studies suggest the relationship between MOE and DM.[7] Our data confirm those findings as only 11% of our MOE patients were non-diabetic. On the other hand, the authors suggest that the presence of DM in MOE patients is far less common than anticipated. In their 11-year analysis, Sylvester et al[8] report that elderly diabetic patients were only 22.7% of all MOE hospitalizations. In their population-based control study of Taiwan, Yang et al[9] report that—while significant—only 54.8% of MOE patients had a prior diagnosis of DM. Diabetes mellitus was present in 74.6% in a study of 355 patients reported by Guerrero-Espejo et al.[10] While often reported, there is a lack of data in the literature regarding the clinical, imaging, and laboratory findings and the treatment course of non-diabetic patients. Are there any differences between diabetics and non-diabetic patients with MOE?

To date, there have been very few reports of this severe form of otitis externa in immunocompetent individuals.[2,5,11-20]

Our findings suggest that non-diabetic patients with MOE have similar clinical presentation and physical findings as diabetics. All of them had otalgia, otorrhea, edema of the external auditory ear canal and

Table 1. Differences Between Diabetic and Non-Diabetic MOE Patients

		Group A	Group B	Total (%)	*P*
		Diabetic	Non-diabetic		
		n = 32	n = 4	n = 36	
Sex	Male	26	1	27 (75)	-
	Female	6	3	9 (25)	
Age	Mean ± SD	77.22 ± 8.17 (min: 61, max: 89)	47.25 ± 3.59 (min: 44, max: 52)	73.89 ± 12.31	**<.001**
	95% CI	74.27-80.16	41.53-52.97	69.73-78.05	
DOH	Mean ± SD	42.41 ± 31.06 (min: 17, max: 155)	10.25 ± 2.63 (min: 8, max: 14)	38.83 ± 30.99	**.049**
	95% CI	31.21-53.60	6.07-14.43	28.35-49.32	
ESR	Mean ± SD	71.06 ± 30.58 (min: 28, max: 120)	63.25 ± 29.19 (min: 37, max: 90)	70.19 ± 30.12	NS
	95% CI	60.04-82.09	16.8-109.7	60-80.39	
WBC	Mean ± SD	8201 ± 1584 (min: 4670, max: 10880)	7505 ± 1836 (min: 5400, max: 9300)	8124 ± 1601	NS
	95% CI	7630-8772	4583-10427	7582-8665	
CRP	Mean ± SD	41.19 ± 25.79 (min: 7.9, max: 94.2)	24.55 ± 17.62 (min: 11.5, max: 49.8)	39.34 ± 25.38	NS
	95% CI	31.89-50.49	3.49-52.59	30.76-47.93	
HbA1c	Mean ± SD	7.97 ± 1.8 (min: 5.6, max: 12.5)	5.1 ± 0.3 (min: 4.7, max: 5.4)	7.6 ± 1.9	**.003**
	95% CI	7.3-8.6	4.6-5.6	7-8.3	
Blood glucose	Mean ± SD	193.3 ± 55.6 (min: 121, max: 369)	86.5 ± 12.9 (min: 74, max: 102)	181.5 ± 62.6	**.001**
	95% CI	173-213	66-107	160-203	

WBC, white blood cell; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; DOH, days of hospitalization; HbA1c, glycated hemoglobin; SD, standard deviation; MOE, malignant otitis externa.

positive Tc 99 findings. Two of them had polyps as half of our total sample. Moreover, all patients had a prior diagnosis of external otitis and exacerbation of their symptoms after failing courses of different antibiotics, until a diagnosis of MOE was considered.

Three cases of non-diabetic patients presented by Unadkat et al[5] had cranial nerve palsies at the time of submission. Liu[13] reports a healthy 60-year-old non-diabetic patient who was treated for MOE after 13 months' symptoms. Orioli et al[14] report a patient with a

Table 2. Characteristics of Non-Diabetic, Non-Immunocompromised Patients

	Patient 1	Patient 2	Patient 3	Patient 4
Sex	Female	Male	Female	Female
Age	52	48	44	45
SBH	13	14	15	14
Major symptoms	All	All	All	All
Minor symptoms	2	2	3	2
WBC	5400	8760	9300	6560
CRP	23.4	11.5	13.5	49.8
TKE	90	87	37	39
HbA1c	5.2	5	5.4	4.7
Blood glucose	92	102	74	78
Pathogen	*Pseudomonas aeruginosa*	*P. aeruginosa*	*P. aeruginosa, Finegoldia magna*	*Staphylococcus aureus, Acinetobacter baumannii*
DOH**	9	10	8	14

SBH, duration of symptoms before hospitalization (days); DOH, days of hospitalization; WBC, white blood cell; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HbA1c, glycated hemoglobin.

diagnosis of MOE after 4 months' symptoms who was treated successfully but revealed central skull base osteomyelitis that presented with cranial nerve palsies at the time of the initial follow-up. Leventhal et al[15] reported an immunocompetent patient with otalgia of 2 months duration that progresses to the bilateral skull base and cervical spine osteomyelitis. In our series, none of the 4 non-diabetic patients had cranial nerve involvement. In a meta-analysis of 8300 cases, Sylvester et al[8] report that DM was associated with CN VII and CN X involvement. The authors suggest that cranial nerve involvement is related to DM and/or is the result of a delayed MOE diagnosis.[5]

Similar to other studies, *P. aeruginosa* remains the most common pathogen isolated in 64% of our patients, both diabetic and non-diabetic followed by *Staphylococcus* species and mycotic pathogens.[2,3,5] In several reported cases of non-diabetic patients, *Aspergillus* and not *Pseudomonas* was the isolated organism.[16-20] A fungal microorganism was isolated in 3 patients of our series who were all diabetic, although larger studies have to be done in order to conclude if there is a strong association between fungal MOE and DM.

Classic inflammatory markers showed increased CRP and ESR in all patients of our series at the time of admission with no statistical significance between diabetic and non-diabetic patients. Surprisingly, none of our patients had an increased WBC count. This observation is not new. Several authors report that ESR and CRP may be useful laboratory markers for the screening of MOE.[21,22]

Our radiological findings suggest that the use of a routine HRCT has limitations (positive findings in 83%), and thus, it should be used in combination with other imaging methods (MRI, Tc-99, and Ga-67). It is known that HRCT and MRI are useful to delineate bone and soft tissue involvement; moreover, the diagnosis of MOE is supported by a positive methylene diphosphonate Tc-99m bone scan and Ga-67 scan. Despite this common practice, one should consider the results of the study conducted by Sturm et al[23] in which they conclude that the sensitivity and specificity of Tc-99m and Ga-67 imaging findings are more limited than once imagined as they provide little anatomic detail, entail high costs and radiation exposure, and are not widely available. By contrast, CT and MRI are widely available and afford excellent anatomic resolution but are neither sufficiently sensitive nor specific as standalone modalities. The authors of the aforementioned study also refer to the usefulness of 18-FDG-PET/CT as a promising hybrid imaging modality for diagnosing and assessing the treatment response in MOE. The authors' opinion is that the combined use of HRCT with other imaging methods gives a favorable outcome for the diagnosis of MOE if PET/CT is not available.[23]

Our findings confirm literature's recommendations that the use of quinolone antibiotic treatment reduces mortality. Oral and topical fluoroquinolones in systemic and targeted treatment of MOE are effective for outpatient treatment. All patients in our series received intravenous antibiotic therapy that was modified by tissue and ear swab culture results. In addition, only 4 patients underwent cortical mastoidectomy. Grandis et al[24] in a literature review concluded that surgical management such as debridement had no role in the treatment of MOE since the advent of fluoroquinolone therapy and therefore suggest the reduction of surgical operations. The author's opinion is that surgical debridements should only be performed in the case of complicated MOE such as "a possible last option" in the failure of conservative treatment. None of our patients received hyperbaric oxygen therapy as it remains a very rarely used treatment option.[8]

Our data also revealed that DM is associated with a longer hospital stay, although the non-diabetic patients had a better response to intravenous antibiotic therapy and 4 times shorter hospitalization than the diabetic patients.

Several studies suggest that mortality is higher in elderly diabetics. In our case series, the 4 patients with MEO who died had a mean age of 72 years. Diabetes mellitus was found to be a significant risk factor for disease-specific mortality in a study of 88 patients conducted by Shavit et al[3] since all patients who died had DM. In the meta-analysis of Sylvester et al.[8] in-hospital mortality was not associated with DM but the elderly were highlighted as the most at-risk age cohort in terms of in-hospital mortality.[8]

CONCLUSION

There seem to be no differences between diabetic and non-diabetic patients with MOE as regards the clinical, imaging, and laboratory findings. The main group of MOE patients remains the elderly diabetics and immunocompromised patients. Although non-diabetic, non-immunocompromised adult patients had a better response to antibiotic therapy and a shorter length of hospitalization, proper diagnosis and timely treatment are essential. A high clinical suspicion for MOE should always raise in cases of otitis externa that fail to respond to a topic and/or oral antibiotic treatment for more than a week.

Ethics Committee Approval: Ethical committee approval was received from Attikon University Hospital (approval ID: IRB 205/05-04-2021).

Informed Consent: Consent was not required as data is anonymous and there was no interference with standard techniques as part of the study.

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