ORIGINAL RESEARCH

Malignant Otitis Externa: Association of Biochemical Markers with Staging of the Disease and Emergence of Methicillin Resistant *Staphylococcus aureus* as a Causative Agent

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Abstract

Background and objectives: Malignant otitis externa (MOE) is a potentially fatal illness that affects the soft tissues of the exterior ear and neighboring structures and has a propensity to advance fast to the skull base and the periosteum. The goals of this study were to demonstrate a clinical association between MOE phases and biochemical markers such as glycosylated Hb (HbA1c), C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) levels, as well as to detect improvements in clinical symptomatology and the emergence of Methicillin resistant *Staphylococcus aureus* (MRSA) as a causative agent.

Methodology: Patients coming to the ear nose throat out patient department (ENT OPD) with diabetes mellitus (DM), otalgia, and ear discharge were given a detailed history and clinical examination. An otoscope was used to examine and look for external canal edema, granulation tissue, bone erosion, and TM perforation. Under aseptic conditions, pus from the external auditory canal (EAC) was collected for culture and sensitivity testing. Baseline HbA1c, ESR, and CRP levels were measured, and high resolution computed tomography (HRCT) temporal bone in the axial and coronal planes was done. The patients were staged using Chandler's clinical pathological staging based on CT and clinical findings. Intravenous course of antibiotics, paracetamol, and local aural flushes were administered. After the first and second months, the patients were asked for a follow-up visit. The otoscopic evaluation was repeated under a microscope. Further under all aseptic conditions, pus from the EAC was collected for culture and sensitivity and HbA1c, ESR, and CRP levels were sent again. Patients was staged afresh as per the Chandler's classification.

Results: A drop in HbA1c levels is an excellent prognostic predictor of the illness. The periodicity of diabetes has little effect on the diseases prognosis. *Pseudomonas aeruginosa* is the most prevalent etiological factor, although MRSA was also witnessed in the culture sensitivity report from these selected patients. A decline was observed in ESR and CRP values after 2 months of treatment.

Conclusion: In conclusion, "MOE is an invasive, potentially life-threatening infection of the external ear" which rapidly advances to the skull base in uncontrolled diabetics and immunocompromised patients. Response to medication can be tracked by ESR, CRP, and glycated HbA1c. The research focuses the need of controlling this infection with medical treatment, emphasizing the fact that surgical care is restricted for stages I, II, and III.

Keywords: C-reactive protein, Diabetes mellitus, Glycosylated Hb, Methicillin resistant *Staphylococcus aureus*, Skull base osteomyelitis.

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Introduction

Malignant otitis externa is a highly aggressive and possibly fatal illness that affects the soft tissues of the exterior ear and neighboring structures, with a proclivity for progressing to the skull base and periosteum.[1] It is more frequent in the older age-group (>60 years) with uncontrolled diabetes and affects males more than females. Malignant otitis externa is a clinical diagnosis based on nocturnal discomfort, exudate, granulations, and edema of the EAC, which is frequently accompanied by a positive and definite bone scan and the detection of micro abscesses intraoperatively. A "positive" bone scan, in combination with the evolution of *P. aeruginosa* on culture, single or multiple cranial nerve palsy, and diabetes or any other immunocompromised state confirms the criteria that enhance the specificity of MOE.[2,3]

Malignant otitis externa is more prevalent in diabetic people because diabetes causes microangiopathy, which leads to inefficient microcirculation and reduced polymorpho–nuclear cell activity. Good glycemic control, as assessed by HbA1c, is essential for effective antibiotic therapy. Non-specific inflammatory indicators such as "CRP and ESR" levels are markedly raised in untreated instances of MOE and can be used to assess therapy response. The ESR is frequently more than 100 mm/hour.[4]

Among diagnostic imaging, "computed tomography (CT) is the most widely performed imaging modality for both diagnosis and follow-up for skull base osteomyelitis (SBO)." The superiority of magnetic resonance imaging in determining the specific anatomical

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location and soft tissue extension in SBO is one of its potential advantage.[5]

Despite breakthroughs in antibiotic therapy, a sizable proportion of the population continues to die from this disease. The Chandler's clinico–pathological grading system may be used to forecast the length of therapy at the time of diagnosis, allowing for more effective use of hospital resources.[6] Moreover, HbA1c, CRP level, and HRCT studies are effective in determining illness remission.

In this study, we hope to demonstrate a clinical association between disease stage and prognostic indicators such as HbA1c and CRP levels, as well as a microbiological assessment that will aid in streamlining treatment outcomes.

Aims and Objectives

- To demonstrate a clinical relationship between MOE stages and biochemical indicators such as HbA1c, CRP, and ESR levels.
- To identify the causative organisms as per the microbiological study and symptomatic improvement in MOE following treatment.

Methodology

This retrospective study was conducted among 32 patients over a period of 2 years in the Department of ENT at a tertiary care hospital in Gurugram, India. This research included patients of both genders aged 15–80 years presenting with MOE and DM.

Those patients with comorbidities such as chronic kidney disease (CKD), hematological malignancies, hepatic dysfunction, chronic granulomatous illnesses such as TB, leprosy, etc., malignant tumors of the external or middle ear, and anemia were excluded from the research.

Patients coming to the ENT OPD with DM, otalgia, and ear discharge were given a thorough history and clinical examination. After obtaining written consent otoscopic examination under microscope was done to look for external canal edema, granulation tissue (Fig. 1), bone erosion, and TM perforation. Under aseptic conditions, pus from the EAC was collected for culture and sensitivity testing. Baseline glycated hemoglobin, ESR, and CRP levels were measured, and HRCT temporal bone in the axial and coronal planes was done.

The patients were staged based on clinical observations and CT results using Chandler's clinic pathological staging (Table 1).

Patients were subsequently put on IV antibiotics up to 6 weeks based on their sensitivity pattern. For pain treatment, IV paracetamol was administered. In the instance of canal edema, local intervention in the form of periodic acetic acid washes and canal packing with 25% glucose and glycerin was carried out. All patients were administered parenteral insulin – actrapid and insulatard – to keep their random blood sugar levels between 160 and 180 mg/dL. In three patients who did not comply to 2 weeks of medical therapy, a Modified Radical Mastoidectomy was performed. The follow-up was done after the first and second months from the date of the initial appointment. During these visits, glycated hemoglobin ESR, and CRP levels will be checked again, and restaging will be done based on clinical criteria.

Results

In our study, the most common age-group affected was between 51 and 60 years (33.3%) followed by above 70 years (30.3%) as shown in Figure 2.

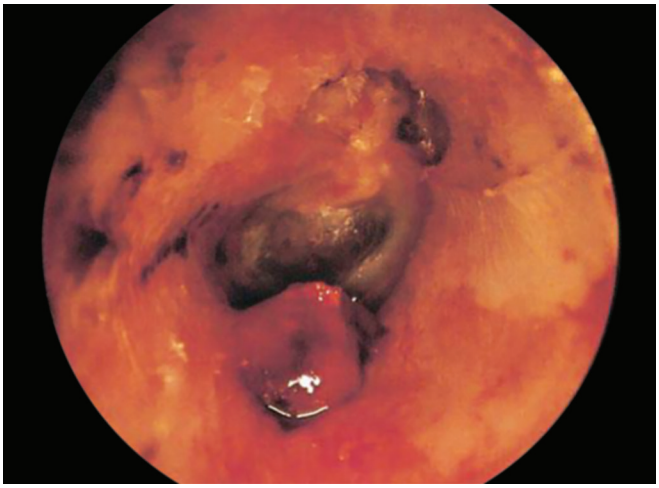

Fig. 1: Oto–endoscopic view of right EAC showing granulations on the floor (arrowed)

Table 1: Chandler's clinic pathological staging

Stage	
I	Clinical evidence of MOE with infection of soft tissues beyond the EAC, but negative Tc-99 bone scan
II	Soft tissue infection beyond EAC with positive Tc-99 bone scan
III	As above, but with cranial nerve paralysis:
IIIa	Single
IIIb	Multiple
IV	Meningitis, empyema, sinus thrombosis, or brain abscess

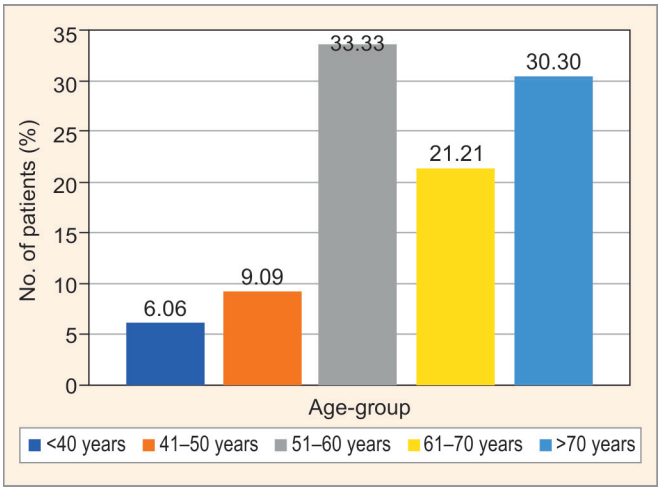

Fig. 2: Age distribution

Males (88%) were more harmed than females (12%). On their first visit to the hospital, all 32 patients (100%) complained of otalgia. After 1 month of antibiotics and analgesics, about 8 patients (out of 32) had chronic symptoms of otalgia, and after 2 months of antibiotics and analgesics, 29 patients were followed up on, with just 1 (3%) having persistent otalgia.

In our study, 2 patients (3%) reported with otalgia lasting more than 6 months, 10 patients (31.25%) presented with otalgia lasting 3–6 months, and 20 patients (66%) presented with otalgia

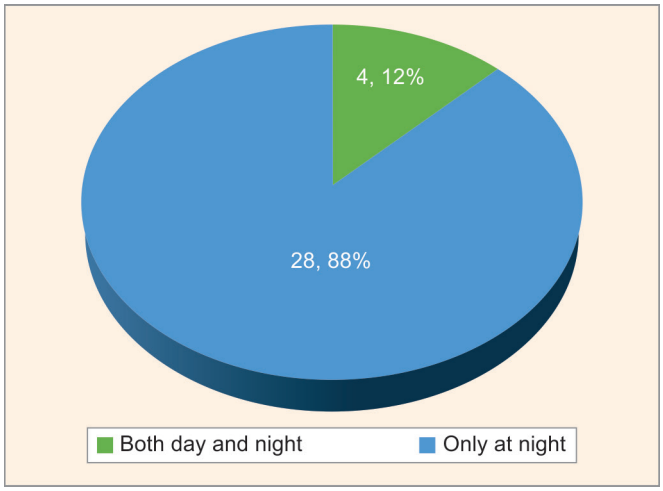

Fig. 3: Diurnal variation of otalgia

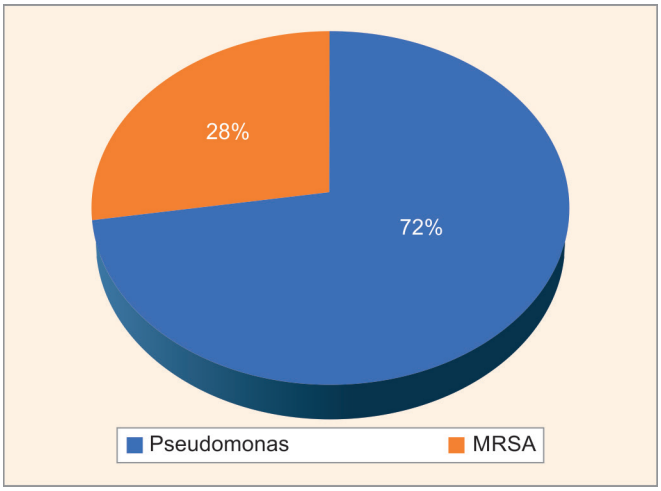

Fig. 4: Pus culture sensitivity of ear discharge

Table 2: Local pathologies encountered in patients of MOE

Local pathologies	*Frequency (n)*
Canal edema	30
Granulation tissue	32
Bone erosion	5
Tympanic membrane perforation	11
Facial palsy	5
Mastoid tenderness	0

lasting less than 3 months. The research group experienced diurnal fluctuation (Fig. 3).

About 31 patients were relieved by analgesics in our study and only 1 patient was not relieved. Out of 32 patients diagnosed to have MOE, 5 patients had facial palsy. Three patients had grade 3 palsy (House–Brackman's classification) and 2 had grade 4 palsy at presentation. In our study, 29 patients (90.62%) presented with ear discharge, and 3 patients (9.38%) had no discharge. Table 2 illustrates the various local pathologies encountered.

Three patients (9.38%) presented with headache on admission. On otological examination under the microscope of 32 patients who presented with the disease 11 patients (34.4%) presented with tympanic membrane perforation, 8 patients (25%) had no perforation and remaining 13 patients (40.6%) tympanic membrane was not visualized. As per the microbiological examination of the pus culture sensitivity of 29 patients with discharging ear showed growth of pseudomonas in 21 patients (72%) whereas the remaining 8 patients (28%) showed growth of MRSA as shown in Figure 4.

Discussion

In this study, the targeted sample size was 32 patients with MOE and diabetes of both the genders in the age-group of 35–80 years with symptoms of otalgia, ear discharge, with or without facial palsy with uncontrolled blood sugars. In a study by Sylvester et al., 90% of the study population belong to the age-group of 40–75 years.[7] According to Hatch et al. study; "malignant otitis externa" is widespread in those over the age of 50, and their findings show that being older correlates with a higher risk of the condition.[8] This was analogous to our study, which found that the majority of patients aged 51–60 years (33.3%) belonged to the age-group 51–60 years, followed by above 70 years (30.3%). Several theories have been postulated for the physiologic association between advanced age and MOE, including diminished ear canal epithelial migration and microvascular illness impairing an appropriate immune response. Comorbidities such as diabetes, which has been related to compromise immune response and microvascular illness, have been correlated to advanced age.

Furthermore, the aging population is more likely to clean their ears owing to dry and itchy skin, which produces local trauma leading to granulations and infection in an environment where the pH is altered due to diabetes, resulting in drop in immune response.

The male-to-female sex ratio in our study was 7:1. Various studies done by Hatch et al.,[8] Guerrero-Espejo et al.,[9] Lee et al.,[10] and Cavel et al.,[11] have proved a male dominance pattern of the disease. This difference may be due to the difference in fat distribution in both sexes, difference in lifestyles pattern, family history, and genetic predisposition. Hence, the propensity of developing complications is more prevalent in a male patient diagnosed with MOE with a pre-existing diabetes.

Nocturnal otalgia, though not pathognomic, is a prevalent feature seen in patients with MOE. Studies done by Guerrero–Espejo et al.,[9] Lee et al.,[10] Cavel et al.,[11] and Kaya et al.,[12] showed that "nocturnal otalgia has been a common mode of presentation due to the preoccupancy" of the patients with daytime activities which divert the attention of the patients from experiencing the pain, and this in turn is noticeable at night when the patient rests. If the patient has associated secondary otitis media, he may experience pain at night due to inactivity of Eustachian tube resulting from restriction of jaw movements and swallowing.

"Diabetes mellitus is the most common comorbidity seen in patients with MOE." Sylvester et al.[7] found that about 55.1% of patients had insulin depended DM and most of them belonged to above-60-years age-group. Lee et al.,[10] Cavel et al.[11] observed hypertension (about 50%) as the second most common comorbidity. In our study, 17 (53.5%) out of 32 patients presented with hypertension.

The symptom of headache in MOE suggests the presence of meningitis, SBO, or intracranial abscess. In our study, the HRCT done in these three patients did not show any intracranial complications. However, this could be attributed to the presence of skull base cellulitis.[12]

Table 3: Comparison of HbA1c

HbA1c	*Mean*	*Standard deviation*	*N*	*p-value*
Baseline	8.468966	1.5448309	29	<0.001
Second follow-up	7.031034	1.4385269	29	

Table 4: Comparison of ESR

ESR	*Mean*	*Standard deviation*	*N*	*p-value*
Baseline	46.03	6.185	29	<0.001
First follow-up	40.93	7.050	29	
Second follow-up	32.00	9.196	29	

The most frequent bacterium responsible for more than 90% of MOE cases is *P. aeruginosa*. Aspergillus can cause MOE in rare cases, and case reports of various Gram-positive and Gram-negative bacteria are also available. Although, in our study, 72% of patients had shown growth of *Pseudomonas* whereas 28% showed growth of MRSA(in total of 29 patients with discharging ear). According to the study by Mittal et al.,[13] the mean pH of normal EAC is significantly more acidic (3.950 ± 1.199) which becomes more alkaline in a diabetic patient in presence of local moisture, *Pseudomonas* flourish at an environment with temperature of 37°C and pH of alkaline range, 7.5–8.5, which predispose the diabetic and immunocompromised patient to develop otitis externa.

In our study, we compared CRP and ESR values of the patients presented with MOE from the first visit up to the third month of the treatment; aware of the fact that HbA1c reflects the 3-month average of plasma glucose concentration, it was repeated on the second follow-up. Here in the analysis of HbA1c, the values from the first visit of the patient are compared with the HbA1c values of the third month. As shown in Table 3, using measured ANOVA test, the variables were compared which clearly showed a significant *p*-value (<0.001) proving that while receiving IV antibiotics, the patient's glycemic control improves dramatically, lowering morbidity and duration of hospital stay.

The reduction in inflammatory indicators decreases insulin resistance and hence improves the glycemic index.

Erythrocyte sedimentation rate is an excellent predictor of therapy response. It is suggested that patients of recurrent MOE should be treated with great care.[5] Several investigations have shown that ESR is considerably raised in conjunction with MOE, frequently reaching 100 mm/h, and it is useful not only in validating the diagnosis but also in monitoring the therapy response. In this study, we compared the ESR value at the initial visit to the ESR values during the two follow-up visits (at the first and second months). According to the ANOVA of the variables, there was a significant drop in the ESR values, which associated with the illness prognosis.

Kaya et al.[12] conducted a similar research with an ESR score of 26 patients which was compared in a span of 6 weeks and observed a statistically significant fall in the ESR values similar to our study (Table 4).

Furthermore, CRP is a circumferential (ring-shaped) pentameric protein present in blood plasma that increases in reaction to inflammation.[14] The normal concentrations in healthy human serum ranges between 5 and 10 mg/L, with concentrations rising with age. Late pregnant women, moderate inflammation and viral infections (10–40 mg/L), active inflammation, bacterial infection (40–200 mg/L), severe bacterial infections, and burns all have larger concentrations. (>200 mg/L).[15] Statistically, CRP does not follow the assumption of normality, and hence we used Friedman test for testing the significance of CRP in the 3 time points. There was a significant reduction between the variables of CRP from first to third visit. In a study by Kaya et al.,[12] the mean CRP levels were found to be 2.54 ± 1.90 mg/dL and in the first examination, CRP levels were found to be increased by 66.7–78.6% which was similar to our study variables (Table 5).

Table 5: Comparison of CRP

		Percentiles			
CRP	*N*	*25th*	*50th (Median)*	*75th*	*p-value*
Baseline	30	2.300	3.100	3.400	<0.001
First follow-up	30	2.100	2.500	3.200	
Second follow-up	30	1.400	2.100	2.350	

Henceforth; "ESR and CRP might be effective laboratory indicators for MOE screening."

In this trial, there was a statistically significant improvement in clinical symptoms that coincided with lower levels of ESR, CRP, and HbA1c. Therefore, ESR, CRP and HbA1c were found to be reliable biochemical markers to assess response to therapy in patient of MOE.

Conclusion

In summation, SBO/MOE is an invasive, lethal infection of the external ear that accelerates promptly to the skull base in uncontrolled diabetics and immunocompromised individuals. Because of its proclivity to spread intracranially, malignant external otitis has a high morbidity-mortality rate, manifesting in osteitis and numerous cranial nerve palsies.

This necessitates an immediate diagnosis and treatment of the infection along with diabetes, which can be accomplished through the use of appropriate antibiotics which crosses the blood-brain barrier and have good bone penetration, regular local treatment, debridement of necrosed bone and granulations, sugar control, and sometimes, aggressive surgical management. The research identified MRSA as an emerging causal factor that runs concurrently with pseudomonal infection, making infection management more difficult.

Furthermore, ESR, CRP, and glycated HbA1c can be used to track therapeutic response. The study emphasizes the need of controlling this infection with medical treatment, exemplified by the fact that the surgical management is constrained for the first, second, and third stage.

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