www.jmscr.igmpublication.org
Impact Factor 5.84
Index Copernicus Value: 83.27
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossref DOI: https://dx.doi.org/10.18535/jmscr/v5i3.105

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

Malignant Otitis Externa: A Clinicomicrobiological Study from a Tertiary Referral University Hospital in South India

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ABSTRACT
Malignant Otitis Externa (MOE) has shown a resurgent trend due to a rise in incidence of type 2 diabetes mellitus in developing countries like India. Classically, Pseudomonas aeruginosa has been implicated as the causative agent and empirical treatment involved Pseudomonas specific antibiotics. Recently, other microbiological agents and polymicrobial infections have been found to be associated with MOE.
Objective: *To analyze the microbiological pattern of MOE and its impact on the treatment and outcome of the disease based on our ten years experience of managing this condition.*
Methods: *A retrospective study of all cases of MOE, treated at a tertiary referral hospital, between 2005-2015, was carried out. Details of patient histories, clinical assessment, management and outcomes were analyzed.*
Results: *In this study, 21 patients diagnosed with MOE, were included. All of them had poor glycemic control and the majority of them had deranged electrolyte levels (18/21) in addition to anemia (20/21). Pus culture from the external auditory meatus revealed different microorganisms, Pseudomonas Aeruginosa(6), Staphylococcus aureus (3), polymicrobial(4), Enterococcus fecalis (1),Candida tropicalis(1). Control of the hyperglycemic status along with correction of electrolyte imbalance and culture directed parenteral antibiotics for a minimum period of 1 week resulted in 95% of patients recovering without sequelae.*
Conclusion: *Early diagnosis and aggressive management are essential for a satisfactory outcome. Parenteral and topical antibiotic therapy should be initiated keeping in mind the diverse microbiological spectrum encountered in this condition. A treatment protocol, specific to this region (tropics), has been developed by us and has proved successful.*
Keywords: *Malignant otitis externa, Skull base osteomyelitis, Pseudomonas aeruginosa, Staphylococcus aureus, polymicrobial infection, Diabetes mellitus, treatment protocol.*

Introduction

Malignant Otitis Externa is a rapidly spreading, life threatening, invasive infection of the skull base originating in the external auditory canal. It is commonly caused by *Pseudomonas Aeruginosa* and is prevalent in the elderly with uncontrolled

diabetes mellitus or in the immuno compromised. Toulmouche, a physician, is credited with first describing this condition in 1838.[1] It was first recognized as a distinct clinical entity by Meltzer and Kelemen in 1959[2]. It was Chandler, who gave the first comprehensive description of the condition in a case series from 1968 to 1974. He coined the term "malignant external otitis" and described the specific clinical characteristics of this disease. At that time, surgery was the mainstay of treatment and it resulted in frequent recurrences and mortality rates approaching 50%.[3] At present, a conservative management protocol, involving culture directed aggressive parenteral antibiotics in higher doses, local debridement and strict glycemic control, has resulted in improved outcomes.

Classically, the presence of Pseudomonas in the affected ear has been considered one of the hallmark features of this disease and has even been an obligatory diagnostic criterion.[4] It was not until 1982 that the first case of non pseudomonal MOE was reported due to *Staphylococcus aureus*.[5] In recent years other bacteria have been reported to cause malignant external otitis, which includes *Proteus mirabilis*, *Klebsiella oxytoca*, *Pseudomonas cepacia*, and *Staphylococcus epidermidis*. Also, fungal colonization has been observed more frequently nowadays, which needs to be kept in mind. Common fungi encountered are Aspergillus species or *Candida albicans*, although other fungi like Scedosporium *apiosperumum, Pseudallescheria boydii*, *Candida ciferri*, and *Malassezia sympodialis* have also been reported.[6]

With the increasing incidence of type 2 diabetes mellitus in developing countries like ours, MOE has shown resurgence. Hence the otolaryngologist needs to be aware of the changing spectrum of the epidemiology and microbiology of MOE and modify the management protocol to suit the individual patient.

Our study will highlight the common clinical findings in these patients, laboratory values which were found to be affected by the disease and how they alter as the condition improves. It will detail the various microorganisms isolated on culture of pus from the external auditory canal and the antibiotic sensitivity and resistance of these isolates. Finally the treatment protocol, which is being followed by us, will be presented. It can be instituted in suspected cases of MOE in a developing country like ours. The aim is to shorten the course and prevent fatal complications in these patients.

Materials & Methods

A total of 21 patients of MOE managed by one consultant in the Department of Otorhinolaryngology and Head and Neck Surgery of a University tertiary care hospital in South India, with a minimum follow up of 12 months, treated from 2005 to 2015 (10 years) were included in this study.

Their case reports were analyzed in detail. Patient's nutritional status, predisposing factors (systemic & local), clinical presentation and initial investigations (Hematology, Imaging, Histopathology) were recorded. Pus swab, from the external auditory canal, was always sent for culture and sensitivity on the patient's first visit to the hospital. The microbiology reports were obtained. Treatment methods, like regular aural toileting, initial empirical antibiotics and then later culture directed antibiotics, glycemic control, electrolyte correction and surgery, to drain microabcesses and remove necrotic bone, were noted. The above data were then analyzed. Based on this data and patient outcome a management protocol has been developed which is currently being followed in our institution leading to better results.

Results

The number of patients identified from our medical records department, with the required documentation and confirmed diagnosis of MOE were 21. The age of the patients ranged from 50 to 83 years, with mean age at diagnosis being 66 years. There were 4 females and 17 males.

Duration of symptoms (nocturnal otalgia/ discharge) ranged from 5 days to 4 months.

All 21 patients presented with predominant symptoms of nocturnal otalgia and discharge from the affected ear. Out of these, 7 patients had cranial nerve involvement of which 6 had isolated lower motor neuron facial palsy and 1 patient had involvement of the 9,10,11 and 12th cranial nerve in addition to the 7th nerve involvement.

All patients were on treatment for Type 2 Diabetes Mellitus (DM). Five patients were on a combination of insulin and oral hypoglycemic agents (OHA) and 16 patients on OHAs alone. The minimum duration of past treatment for DM was 5 years. All our patients had elevated blood sugars (Random/Fasting/Post Prandial) and glycosalated hemoglobin (HbA1C) values at presentation.

Out of them, 6 patients had hemoglobin values below 10gm/dl. All had hemoglobin levels below 12gm/dl except for one patient with hemoglobin of 14gm/dl.

Serum electrolytes were deranged revealing hyponatremia and hypokalemia in 18 out of 21 patients.

Based on the weight and height recorded in our patients' charts the Body Mass index was calculated. All of them had BMI within the normal range, except for one patient who was found to be obese.

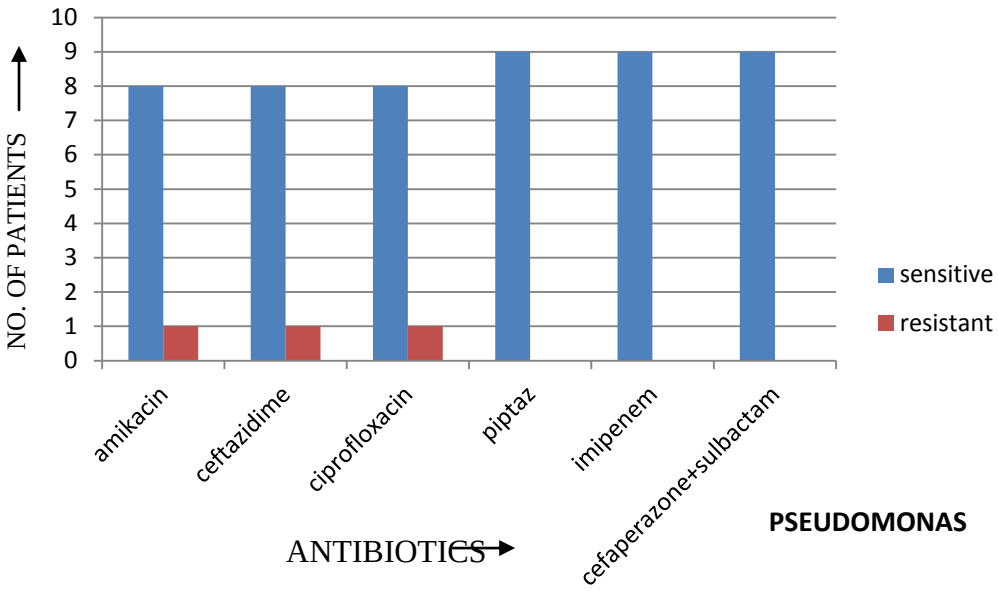
All patients on admission had a swab taken of their ear discharge which was sent for culture and sensitivity testing. (TABLE 1)

There were 5 patients whose cultures grew *Pseudomonas aeruginosa* alone. *Staphylococcus aureus* along with *Pseudomonas* grew in 3 patients. One patient had *S. aureus* alone on culture. Two patients had *Candida tropicalis* in their culture of which one also grew *S. aureus* in addition to Candida. One patient had culture that grew *Enterococcus fecalis* during initial treatment but later, on follow up, developed fungal infection. Culture was negative in 6 patients. In the nine patients with *Pseudomonas* grown on culture, either alone or in combination, the isolates were sensitive to one or more of the first line antibiotics against Pseudomonas like Ciprofloxacin, Ceftazidime, Piperacillin/ Tazobactam combination, Cefoperazone/ Sulbactam combination, Imipenem and Amikacin. However, one isolate showed resistance to Ciprofloxacin and Amikacin and another patient had an isolate resistant to Ceftazidime. (GRAPH 1)

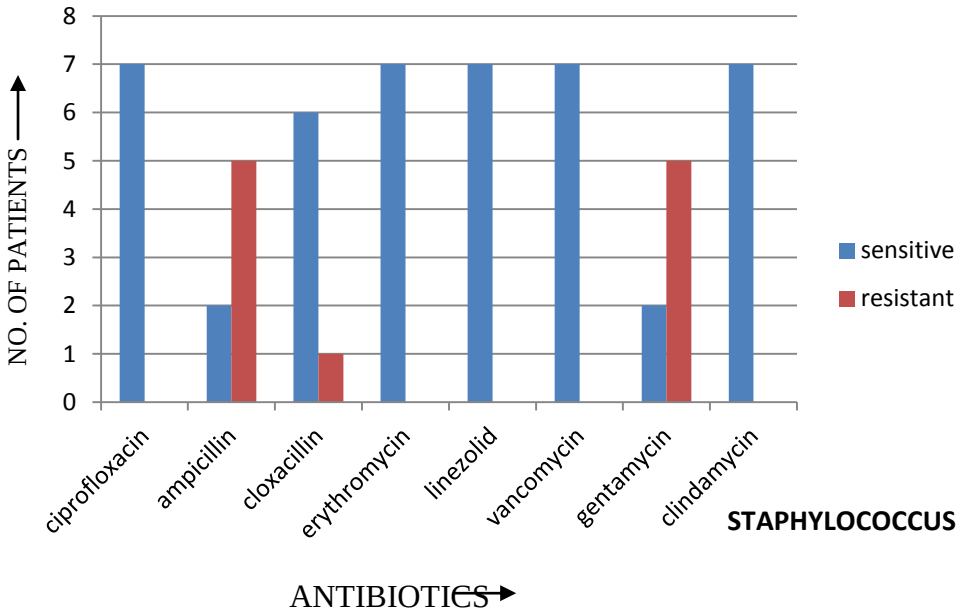
In the seven patients with Staphylococcus in culture, either alone or as part of the polymicrobial infection, the Staphylococcus isolate showed sensitivity to Ciprofloxacin, Clindamycin, Erythromycin, Linezolid and Vancomycin. Five were resistant to Ampicillin and Gentamycin. (GRAPH 2)

Table 1: Organisms Isolated in Each of Our Patient in This Study

Patient no.	Organism isolated on culture
1	*Pseudomonas aeruginosa, Staphylococcus aureus*
2	No growth
3	*Pseudomonas aeruginosa, Staphylococcus aureus*
4	*Pseudomonas aeruginosa*
5	No growth
6	No growth
7	*Pseudomonas aeruginosa*
8	No growth
9	*Pseudomonas aeruginosa*
10	*Staphylococcus aureus*
11	*Candida tropicalis, Staphylococcus aureus*
12	*Candida tropicalis*
13	*Pseudomonas aeruginosa*
14	*Staphylococcus aureus*
15	*Pseudomonas aeruginosa*
16	*Enterococcus fecalis*
17	No growth
18	*Staphylococcus aureus*
19	No growth
20	*Pseudomonas aeruginosa Staphylococcus aureus*
21	*Pseudomonas aeruginosa*



Graph 1 Antibiotic Sensitivity Pattern of *Pseudomonas Aeruginosa* Isolated on Culture



Graph 2 Antibiotic Sensitivity Pattern of *Staphylococcus Aureus* Isolated on Culture

Table 2: Treatment Protocol For Malignant Otitis Externa

		INVESTIGATIONS
DAY 1	A comprehensive physical evaluation and lab workup is done. Patient is admitted. Parenteral antipseudomonal, antistaphylococcal antibiotics+ Topical antibiotic/antifungal medication started. Endocrinologist consultation for glycemic control. Maintenance of nutritional status with appropriate diet and exercise. Pain control with intravenous(IV) analgesia.	Culture & sensitivity of pus from affected ear Complete blood counts Fasting blood sugar(FBS), post prandial blood sugar(PPBS),HbA1C Serum electrolytes Renal function tests, Liver function tests
DAY 2	Review with investigation reports Institute appropriate treatment towards glycemic control, electrolyte imbalance and any fresh symptoms. Daily otomicroscopic suction toileting of ear.	Monitor Capillary blood glucose(CBG)
DAY 3	Review with culture reports and monitoring of other parameters. Antibiotics changed if indicated. If culture is negative, suspect fungal infection. If granulations found biopsy for Histopathological examination. Daily otomicroscopic suction toileting of ear.	Monitor CBG Swab of discharge for fungal smear study. Biopsy of granulations
DAY 4	Reduce IV analgesia if indicated. Start topical antifungal if fungal smear is positive Oral antifungal in cases of aggressive fungal infection. Imaging is done if indicated. Daily otomicroscopic suction toileting of ear.	Monitor CBG HRCT temporal bone
DAY 5	Consider surgical intervention, if condition is not improving, to remove necrotic tissue and drain microabcesses. Also culture swab can be repeated. Alter antibiotics according to culture report. Correct electrolyte imbalance & anemia if present.	Monitor CBG Repeat electrolytes, hemoglobin Repeat culture swab
DAY 6	Review investigations Correct electrolyte imbalance & anemia if present.	
DAY 7	If all parameters are normal patient can be discharged with oral antibiotics. Advise for regular follow up – weekly for 1 month & monthly for 12 months.	Follow up with FBS,PPBS Repeat culture swab can be done to monitor patient.

Discussion

MOE is a rapidly spreading infection, which typically originates at the bony cartilaginous junction of the external auditory canal. It starts as cellulitis of the external auditory canal that progresses to chondritis or osteitis and spreads through the fissures of Santorini to the adjoining deep periauricular tissue and then to the skull

base. The most frequently involved cranial nerve is the facial nerve, at the point where it exits through the stylomastoid foramen. Subsequently, glossopharyngeal, the vagus, and the accessory nerves get affected as they exit through the jugular foramen, and hypoglossal nerve as it exits through the hypoglossal canal. The disease can also invade the temporo mandibular joint and greater wing of sphenoid. Contiguous spread to the meninges, brain, sinuses, and parotid can rarely occur .[6]

Typically MOE is seen in the elderly, who are suffering from diabetes mellitus. It can also occur in younger individuals, probably due to prevalence of early onset of diabetes, as well as immunocompromised and HIV positive patients. In our case series, the age ranged from 50 to 83 years, with the majority in the 6th decade. The male to female ratio was 7:1 and all of them had uncontrolled diabetes at the time of presentation. This is typical of the presentation of MOE which has classically been described as a disease of elderly, male, diabetics.[3]

The most common symptom for which they sought their initial consultation was nocturnal otalgia and ear discharge. The average duration from onset of symptoms to presentation at our clinic was 60 days. Pain and tenderness occurs when the periostium is involved and bone erosion commences. Patient usually seeks ENT consultation at this point in time, as the nocturnal pain disturbs sleep.

About 50% of patients gave a clear history of prior aural irrigation/toileting or of having damaged the skin of external auditory canal by self cleaning of the external auditory canal due to itching in the ear. Thus it can be considered a local predisposing factor.[1,2] Also the climate of South India, which is hot and humid, provides an ideal milieu for bacteria and Fungi to grow in the damaged skin. Fungal infections of the external auditory canal, usually with Candida and Aspergillus are very common[3].

Seven out of the 21 patients had associated lower motor neuron facial palsy. Otoscopy showed granulations in the external auditory canal in all the patients. Three patients also had multiple cranial nerve palsies involving the 7,9,10 and 12 cranial nerves.

Nine patients were on treatment for hypertension in addition to their diabetic status. Two patients also had anemia and one patient had chronic kidney disease. This coupled with hyperglycemic status, resulted in immunodeficiency and microangiopathy leading to rapid development of symptoms, including facial palsy. Hyponatremia and hyperkalemia were seen in 18 out of the 20 patients. These factors had to be corrected along with anti microbial treatment as it can influence the successful outcome of the disease. As patient condition improved the glycemic status, hemoglobin values and electrolytes also reverted to normal.

In our institution, we routinely send swab of the ear discharge for gram staining, culture & sensitivity, and fungal smear study before initiating treatment. In the present study, many patients had mixed flora consisting of *Pseudomonas aeruginosa, Staphylococcus aureus* and fungi, unlike other studies from Europe and the United States, where the predominant organism was Pseudomonas only. [4] Six of our patients revealed no growth on initial culture itself. This may occur if these patients have already been treated with oral/intravenous/ topical antibiotics elsewhere. Here again we stress the importance of obtaining culture swab reports before initiating specific antibiotic therapy.

In our series we found no correlation between the different microbiological agents isolated on culture and clinical course or outcome of the disease.

Initially, anti pseudomonal third-generation Cephalosporins, Penicillins and Aminoglycosides were the mainstay of medical treatment. In the late 1980s Ciprofloxacin, an antipseudomonal flouroquinolone that could be administered orally, became available and since then has commonly been used as a first-line empiric treatment for MOE.[5,6] However, the widespread and often indiscriminate use of ciprofloxacin in the treatment of more simple infections (common

cold) and simpler ear infections has lead to an emerging resistance of the common pathogen (*P.Aeruginosa*) to this drug.[7] Now, also with the increasing frequency of non pseudomonal MOE, ciprofloxacin may not always be an effective treatment, as it has poor gram-positive coverage[7].

All our patients were hospitalized and received parenteral (intravenous) antibiotics along with concomitant topical antibiotics that provided adequate cover against *P. aeruginosa* and *S. aureus*. Subsequently the antibiotic therapy was modified according to the pus culture reports.

Pus culture reports revealed that the 9 patients with *Pseudomonas* isolate were sensitive to most of the first line antibiotics except for one patient who was resistant to ciprofloxacin and ceftazdime. This patient was treated with piperacillin/ tazobactam combination. Six out of our 7 patients with *S. aureus* infection were also treated with piperacillin/tazobactam combination. Oral clindamycin was added after discharge if it was *S. aureus* infection alone and oral ciprofloxacin, if it associated with *Pseudomonas* infection. One patient with *S. aureus* alone on culture received parenteral Amikacin along with oral Clindamycin on discharge. The two patients with *Candida* on culture were treated with an antipseudomonal parenteral antibiotic along with clotrimazole ear drops. In case of persistent fungal growth, as seen in 4 of our patients on follow up, oral antifungals like Itraconazole were prescribed.

Antibiotic therapy was supplemented with regular and meticulous otomicroscopy and aural toileting. Ear swab culture was repeated in many of our patient to detect any additional infectious organ-isms which often developed during the course of the treatment. Accordingly the antibiotics were modified to cover the polymicrobial infection.

On discharge, the antibiotics continued, either parenteral or oral, depending on the severity of the infection. Patients were routinely followed up in the outpatient department for an average of upto 12 months. Radionuclide studies like serial Gallium-67 scans have been recommended to monitor treatment response[6]. In our series, we used serial High Resolution Computed Tomography (HRCT) scans of the temporal bone, when clinically indicated, to assess the spread of disease. Resolution of infection was determined clinically based on symptomatic improvement, disappearance of granulations, recovery of cranial nerve function and also laboratory parameters (total leukocyte counts, erythrocyte sedimentation rate, serum electrolytes, blood glucose, and negative culture of ear discharge).

All our patients had a satisfactory clinical improvement and repeat cultures did not yield any growth. Only one patient (Patient 16) had a prolonged infective course and yielded Candida on culture during follow up. She was treated with an oral antifungal in view of her clinical findings and protracted course. A summary of our treatment protocol is provided. (TABLE 2)

Conclusion

Malignant otitis externa is not an uncommon condition especially in a developing country like ours. Early clinical diagnosis along with appropriate investigations to confirm and direct the treatment should be carried out. Microbiolo-gical examination of Pus from the ear should be mandatory as *Pseudomonas aeruginosa* is not the only organism isolated from these patients but polymicrobial infection is also increasingly observed and antibiotic therapy should be tailored based on culture sensitivity report. Fungal infection, which can be isolated or superadded, should also be kept in mind. A treatment protocol, involving culture directed parenteral antibiotics for a minimum of one week followed by oral and topical antibiotics for a minimum of 6 weeks or as dictated by serial cultures, should be the core of management of malignant otitis externa. In addition regular aural toileting, intensive glycemic control and correction of electrolyte imbalance and nutritional deficiencies need to be done. We rely on clinical assessment and serial cultures during follow up to determine disease resolution. Patients should be regularly followed up.

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