

Original Research Article

A study on correlation between clinical prognostic markers glycated hemoglobin, erythrocyte sedimentation rate and C-reactive protein levels and the stage of disease in malignant otitis externa

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ABSTRACT

Background: Objectives of the study were to establish a clinical correlation between the stages of MOE and biochemical markers namely glycated Hb (HbA1c), C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) levels, to identify improvement in clinical symptomology in MOE following treatment and to correlate with the duration of diabetes mellitus with treatment outcome.

Methods: Patients with diabetes mellitus, otalgia and ear discharge presenting to ENT OPD were subjected to detailed history and clinical examination. Otoscopic examination was done. Pus from the EAC was taken for culture and sensitivity. Baseline glycated Hb, ESR and CRP levels and HRCT temporal bone in axial and coronal planes was done. According to clinical findings and CT findings the patients were staged using chandler's staging. Patients were followed up after 1st and 2nd month and otoscopic examination with blood tests was repeated and staged accordingly.

Results: Fall in the levels of glycated HbA1c serves as a good prognostic indicator of the disease. Duration of diabetes has no significant impact on the disease prognosis. Most common etiologic agent is *Pseudomonas aeruginosa*. In spite of improvement in clinical features and inflammatory parameters there was no improvement in clinical staging with treatment. There was a significant fall in ESR and CRP values after treatment for 2 months with antibiotics and analgesics.

Conclusions: The study highlights the need to control infection with medical line of treatment which can be monitored by ESR, CRP and glycated HbA1c and that the role for surgical management is limited for stage 1, 2 and 3.

Keywords: Malignant otitis externa, Positron emission tomography-computerized tomography, Single photon emission computed tomography, Skull base osteomyelitis.

INTRODUCTION

Malignant otitis externa (MOE) is an aggressive and potentially life-threatening infection which affects the soft tissues of the external ear and surrounding structures and has the propensity to rapidly spread to the skull base and the periosteum.¹

In 1836 the first case was reported in the literature and because of its high mortality the term 'malignant otitis externa' was coined in 1968.^{2,3}

MOE is a clinical diagnosis made on the basis of pain, exudate, granulations and edema of the external auditory canal often supported by a positive bone scan and intraoperatively the presence of micro abscesses.

The CRP and ESR levels are nonspecific measures of inflammation that are significantly elevated in untreated cases and are useful parameters which is used to measure response to treatment. The ESR is often over 100 mm/hour.¹¹

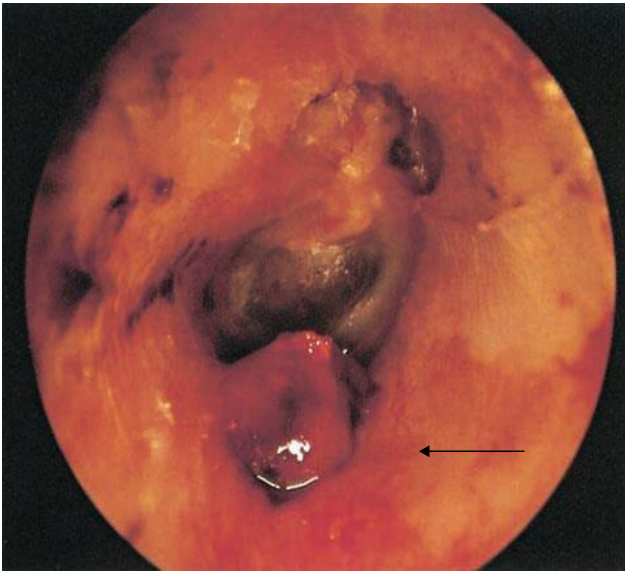


Figure 1: Otoendoscopic view of right external auditory canal of granulations of the floor (arrowed).

Radiological investigations

Among the radiological investigations the most commonly used imaging modality for both diagnosis and follow-up by clinicians for skull base osteomyelitis is computerized tomography (CT).¹⁶ It is the easiest and fastest method to acquire an overview of the mastoid region. High-resolution CT is widely used in the evaluation of bone erosion and demineralization.

Technetium (Tc-99m) radionuclide bone scans are superior to high-resolution computed tomography (CT) scans in that it will detect bony involvement even before the bony destruction.^{1,23,24} The isotope is absorbed by osteoclasts and osteoblasts that continue remodeling even after the infection has resolved, so the scan may remain positive for up to 9 months. As such, Tc-99m is only useful for detecting initial bony involvement.¹

Gallium (Ga-67) is a more sensitive monitor of infection as it is absorbed by leukocytes. The scan which quickly returns to normal after the infection has resolved is a good indicator to determine when to terminate treatment.^{24,25} It should be remembered that Ga-67 is taken up by any inflammatory process, including simple otitis externa and it is useful for monitoring rather than diagnosis.²²

To summarize, the radiological workup for a new case of suspected SBO would be a combination high-resolution CT and a separate PET-MRI (T1, T2, T1-FS-GADO, DWI) in case a hybrid PET-MRI scanner is not available at the hospital then a FDG-PET-(HR) CT and separate MRI (T1, T2, T1-FS-GADO, DWI) would be the preferred mode of workup.

The combination of FDG-PET and either MRI / CT can then also be used for follow-up.

Hematological investigations

CRP is an annular (ring-shaped), pentameric protein found in blood plasma, whose levels rise in response to inflammation. It is an acute-phase protein of hepatic origin that increases following interleukin-6 secretion by macrophages and T cells. Its physiological role is to bind to lysophosphatidic acid expressed on the surface of dead or dying cells (and some types of bacteria) in order to activate the complement system.⁶

Normal concentration in healthy human serum is between 5 and 10 mg/l, increasing with aging.⁸ Higher levels are found in late pregnant women, mild inflammation and viral infections (10-40 mg/l), active inflammation, bacterial infection (40-200 mg/l), severe bacterial infections and burns (>200 mg/l).⁸

Compared to ESR, CRP is a more sensitive and accurate reflection of the acute phase response. ESR may be normal while CRP is elevated. CRP returns to normal more quickly than ESR in response to therapy.⁹ ESR and C-reactive protein levels correlated with disease activity and can be used to monitor progress.¹⁰ CRP combined with appropriate clinical and radiological investigations is a useful biomarker in assessing disease resolution.¹¹

Glycated hemoglobin (hemoglobin A1c, HbA1c, A1C, or Hb1c; sometimes referred to as Hb1c or HGBA1C) is a form of hemoglobin that is measured primarily to identify the three-month average plasma glucose concentration. The test is limited to a 3-month average because the lifespan of a red blood cell is four months (120 days).

It is formed in a non-enzymatic glycation pathway by hemoglobin's exposure to plasma glucose. In general, the reference range (that is found in healthy young person), is about 30-33 mmol/mol (4.9-5.2%).¹⁴

The erythrocyte sedimentation rate (ESR), also called as sedimentation rate or Westergren ESR, is the rate at which red blood cells sediment in a period of one hour. It is a common hematology test, and is a non-specific measure of inflammation.

ESR ranges from 12-24 mm/hr normally in adults.¹⁵ The ESR is a good indicator of treatment response. It is recommended to be meticulous in treatment of cases with recurrent malignant otitis externa.¹⁶ The ESR is often 100 mm/hr in MOE.¹⁷

METHODS

Study design

The study design was of prospective study (validation/cohort study).

Source of data

The study was conducted in the department of ENT and head neck surgery, at St. John’s medical college hospital, Bengaluru, Karnataka from June 2018 to May 2019.

Inclusion criteria

Patients of both sexes in the age group of 15-80, presenting with MOE and DM were included in the study.

Exclusion criteria

Patients with co-morbidities like-CKD, haematological malignancies, hepatic dysfunction, chronic granulomatous diseases like tuberculosis, leprosy etc., malignant tumours of the external or middle ear and anaemias were excluded from the study.

Sample size and sampling methodology

Sample size was 32.

Minimum required sample size, $n = z^2 p(1-p) / d^2$

Where Z=The standard normal variate corresponding to 5% level of significance=1.96 (constant value), p=prevalence /average admission of MOE patients from OPD (approx. 2 per month) d=error (since 95%) 0.05. i.e., $Z^2 P(1-P) / d^2 = (1.96)^2 \times 0.02 (1-0.02) / (0.05)^2 = 30$.

After considering 10% loss to follow up, around 32 patients were required to include in the study (Using N-Master interface software).

RESULTS

At the first visit to hospital all 32 patients (100%) presented with otalgia, after 1 month of antibiotic therapy and analgesics about 8 patients (out of 32) 25% had persistent complaints of otalgia and after 2 months of antibiotics and analgesics 29 patients followed up out of which only 1 (3%) had persistent otalgia.

In our study 2 patients (3%) presented with otalgia of duration more than 6 months, and about 10 patients (31.25%) presented with otalgia of duration lasting from 3 to 6 months and 20 patients (66%) presented with otalgia of less than 3 months duration. 29 patients (90.62%) presented with otalgia only at the night and 3 patients (9.38%) presented with otalgia both day and night

Nocturnal otalgia though not path gnomonic is a common feature seen in patients with malignant otitis externa. Studies done by Kaya et al, Guerrero-Espejo et al, Lee et al, Cavel et al showed that nocturnal otalgia has been a common mode of presentation.⁵ The studies quoted above are in conformity with our study in which 29 patients

(90.62%) presented with otalgia only at the night and 3 patients (9.38%) presented with otalgia both day and night, thus all the 32 patients (100%) had experienced pain in the night and 3 patients had pain throughout the day.

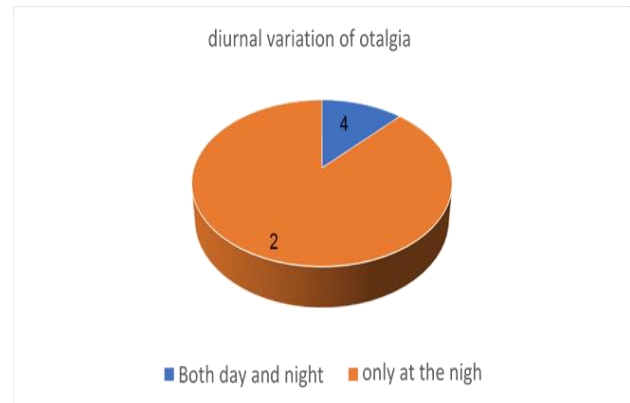


Figure 2: Diurnal variation of otalgia.

Table 1: Duration of ear discharge.

Duration of ear discharge (months)	No. of patients	Percentage (%)
<3	20	69
3-6	7	24.13
>6	2	6.9
Total	29	100

The 29 patients (out of 32) who presented with ear discharge 20 patients (69 %) had ear discharge of duration less than 3 months

Out of the 29 patients who presented with ear discharge (out of 32), 16 patients (55%) had grown skin commensal, 5 patients (17%) had pseudomonas grown in the pus culture 8 patients (27%) had no growth.

DISCUSSION

Malignant otitis externa (MOE) is an aggressive and potentially life-threatening infection which affects the soft tissues of the external ear and surrounding structures and has the propensity to rapidly spread to the skull base and the periosteum.¹

Demographic profile of the study population

Age distribution

Most common age group of MOE patients.

Table 2: Age distribution.

Studies	Age group (years)
Study by Hatch et al ⁷	>50
Our study	51 to 30

According to the study conducted by Hatch et al, malignant otitis externa is common in the age group of >50 years and their study proved that increase in age significantly correlated with the incidence of the disease.⁷ This is comparable with our study, which shows that the greatest number of patients age belong to age group 51 to 60 years (33.3%) followed by >70 years (30.3%).

Gender distribution

The gender proportion of the current study is 7:1, for males and females. Various studies done by Hatch et al, Guerrero-Espejo et al, Lee et al, Cavel et al¹², also prove a male preponderance of the disease.¹⁰⁻¹² A study done by Lee et al which recruited 38 patients had 27 men (71%) and 11 females (29%) which is at par with our study that comprised of 28 males (88%) and 4 females (12%). This wide difference in disease prevalence can be directly attributed to the increased prevalence of diabetes in men compared to women counterpart who have the same BMI. Hence a male patient with MOE is more likely to develop complications related to the disease and uncontrolled diabetes.

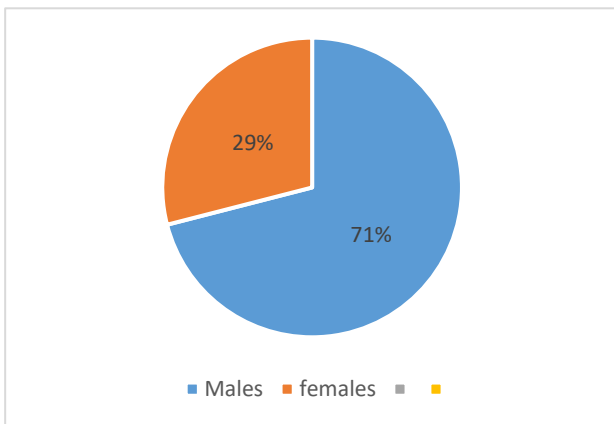


Figure 3: Gender distribution.

Occupation of patients

Although an Indian study done by Prasannakumar revealed the emergence of malignant otitis externa as a common disease in a developing country like India there are no studies which correlate between the disease and the occupation which in turn reflects upon the financial status and knowledge of the patient. In our study we found that there is a significant difference in the incidence of disease and the occupational status of the patient as the greatest number of patients belong to the unemployed or retired (51%) category, followed by clerical/shop owner (31.25%), unskilled worker (15.62%) and professional (3.12%).

Otalgia

Osteitis of the external auditory canal, is the common cause of otalgia in a patient with malignant otitis externa.

In our study 2 patients (3%) presented with otalgia of duration more than 6 to 12 months, and about 10 patients (31.25%) presented with otalgia of duration lasting from 3 to 6 months and 20 patients (66%) presented with otalgia of less than 3 months duration

Comorbidities in malignant otitis externa patients

Diabetes mellitus is the most common comorbidity seen in patients with malignant otitis externa. In the addition to DM the other comorbidities in our study were hypertension 17 (53.5%), thyroid disorders (hypothyroidism) 2 (6.25%), CVD 2 (6.25%), CAD 3(9.38%) and systemic lupus erythematosus (immunological diseases) 1 (3.12%). In studies done by Lee et al, Cavel et al it was observed that hypertension (about 50%) is the second most common co comorbidity condition.

One interesting finding that we encountered in our study is the prevalence of thyroid disorders in a MOE patient which was 2 (6.25%) out of 32 and there is paucity of literature about the relationship between thyroid disorders and MOE. About 50% of patients presented to us had diabetes, hypertension and thyroid disorders.

Micro-organisms grown in culture

Pseudomonas aeruginosa is the most common bacteria responsible in over 95 percent of cases of MOE. Rarely, *Aspergillus* can cause malignant otitis externa and single case reports of other gram-positive and Gram-negative bacteria also exist.¹

Other rare bacteria's (*S. aureus*, *P. mirabilis*, *K. oxytoca*, *P. cepacia*) *orfungi* (*Aspergillus*, *Pseudallescheria*, *Candida*, *Malassezia*) are also found.

Culture from our study showed similar results in our study in which out of the 29 patients who presented with ear discharge (out of total 32), 20 patients (69%) had grown *pseudomonas aeruginosa*, 5 patients (17%) had *Staphylococcus* grown in the pus culture, 4 patients (13.7%) had no growth. Which further reinforces the fact that *pseudomonas* is the organism pathognomonic to the disease.

HbA1c

Glycated hemoglobin (haemoglobinA1c, HbA_{1c}, A1C, or Hb_{1c}; sometimes referred to as Hb_{1c} or HGBA1C) is a form of hemoglobin that is measured primarily to identify the three-month average plasma glucose concentration. The test is limited to a three-month average because the lifespan of a red blood cell is four months (120 days).

Table 3: Comparison of HbA1c.

HbA1c	Mean	S. D.	N	P value
HbA1C 0	8.468966	1.5448309	29	
HbA1C 01	7.693103	1.4901896	29	<0.001
HbA1C 02	7.031034	1.4385269	29	

Here in the analysis of HbA1c the values from the first visit of the patient of the patient is compared with the HbA1c values of the successive second and third month. And using measured ANOVA test the variables were

compared which clearly showed a significant $p < 0.001$ which proves that on treatment with IV antibiotics the glycemic control of the patient also improves significantly and thus reducing their morbidity and length of hospital stay, this may be due to the fall in inflammatory markers which in turn reduces the insulin resistance and hence improving the glycemic index.

Duration of diabetes with disease correlation

The duration of diabetes was compared with the mean HbA1c, CRP and ESR values of two months.

Table 3: Duration of diabetes with disease correlation.

Variables	Name of the test	Median	Quantiles		Correlation coefficient	P value
			25%	75%		
HbA1c 0-HbA1c 02	Spearman's rank correlation	1.3	0.7	2.1	0.189 (Spearman's correlation)	0.325
CRP 0-CRP 02	Spearman's rank correlation	1	0.4	1.1	0.189 (Spearman's correlation)	0.323
ESR 0-ESR 02	Spearman's rank correlation	12	10	2.1	0.111 (Spearman's correlation)	0.565

It was observed that the duration of diabetes has no significant impact on the disease prognosis which was evaluated by the status of the various prognostic markers. The duration of DM and the patient's serum glucose levels were believed to be related to the prognosis of MOE.

ESR

The ESR, also called as sedimentation rate or Westergren ESR, is the rate at which red blood cells sediment in a period of one hour. It is a common hematology test, and is a non-specific measure of inflammation.

Table 4: Comparison of ESR.

ESR	Mean	S. D.	N	P value
ESR 0	46.03	6.185	29	
ESR 01	40.93	7.050	29	<0.001
ESR 03	32.00	9.196	29	

Measured ANOVA of the variables it was observed that there was a significant fall in the ESR values which correlated with the disease prognosis. A similar study was done by Kaya et al the ESR value of 26 patients was compared in a span of 6 weeks and observed a statistically significant fall in the ESR values similar to our study.

CRP

CRP is an annular (ring-shaped), pentameric protein found in blood plasma, whose levels rise in response to inflammation.

Table 5: comparison of CRP.

CRP	N	Percentiles			P value
		25 th	50 th (Median)	75 th	
CRP 0	30	2.30	3.100	3.4000	
CRP 01	30	2.10	2.500	3.200	<0.001
CRP 03	30	1.40	2.100	2.350	

In this study there was a simultaneous improvement in clinical symptoms coinciding with the falling levels of ESR, CRP and HbA1c and it is shown to be statistically significant.

Limitations

Data of patients who went against medical advice and among the patients who died due to other medical complications were lost to follow up after discharge, as a result of which their outcome could not be monitored.

CONCLUSION

Most number of patients belong to age group 51 to 60 years (33.3%). The gender proportion of the study is 7:1, for males and females. A significant number of patients belong to the unemployed or retired (51%) category. Fall in the levels of glycated HbA1c serves as a good prognostic indicator of the disease as proved by measured ANOVA test which showed a significant $p < 0.001$. The duration of diabetes has no significant impact on the disease prognosis as proved by the Spearman's rank correlation which showed a p value greater than 0.3. The chief complaint of most of the patient was nocturnal

otalgia which subsided on IV antibiotic and IV paracetamol and simultaneous control of blood sugars and with surgical intervention in 3 patients. The comorbidities seen in the patient was DM-32 (100%), hypertension 17 (53.5%), thyroid disorders (hypothyroidism) 2 (6.25%), CVD 2 (6.25%), CAD 3 (9.38%) and systemic lupus erythematosus (immunological diseases) 1 (3.12%). The most common etiologic agent is pseudomonas aeruginosa. Culture from our study showed similar results in which out of the 29 patients who presented with ear discharge (out of total 32), 20 patients (69%) had grown pseudomonas aeruginosa, 5 patients (17%) had staphylococcus grown in the pus culture, 4 patients (13.7%) had no growth. There were 5 patients in stage 1, 21 patients had stage 2 disease and 6 patients belong to stage 3 in our study it was noted that there was no improvement in clinical staging with treatment. There was a significant fall in ESR and CRP values after treatment for 2 months with antibiotics and analgesics.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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