

Association of Comorbid Conditions with Six-month Survival and Disease Outcome in Patients of Necroinflammatory Otitis Externa

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ABSTRACT

Objective: To determine association of gender, causative organisms, control of diabetes, facial paralysis, infectious agent, and hearing loss with disease outcome, in terms of six-month improvement of symptoms, static condition or expiry of patients presenting with necroinflammatory otitis externa (NOE).

Study Design: Descriptive study.

Place and Duration of Study: ENT Department in collaboration with Pathology Department, KEMU/Mayo Hospital, Lahore from 2016 to 2019.

Methodology: Patients with NOE were inducted. Studied variables included age at presentation, gender, diabetes, glycated hemoglobin (HbA1c) levels, comorbid conditions, facial nerve involvement, hearing loss, CT and biopsy findings, and causative organisms; and their association with outcome was observed with significance at $p < 0.05$.

Results: Out of 28 patients, there were 17 males (60.7%) and 11 females (39.3%). Association between gender and survival showed that 41.2% (7) males and 27.3% (3) females survived; and 23.5% (4) males and 1 (9.1%) female expired within six months of diagnosis. Thinning of temporal bone (2/5=40%) was common among the expired patients. Twenty percent (1/5) patients diagnosed with squamous cell carcinoma and 80% (4/5) with granulation tissue (GT) expired ($p=0.543$). All ten patients (100%) that improved had mild to moderate hearing loss ($p < 0.001$). Among expired group, 80% (4/5) had HbA1c of more than 7 and 20% (1/5) had good control of diabetes. *Aspergillus* (2/5=40%) and *Pseudomonas* (1/5=20%) were the commonest among expired patients; *Staphylococcus* (6/10=60%) and *Pseudomonas* (3/10=30%) infections were more frequent among the survived ($p=0.005$).

Conclusion: Previously pseudomonal infection was described as the only causative agent of NOE. This study showed a rising community-acquired disease with *Staphylococcus aureus* 6/10 (60%) and *Pseudomonas* 3/10 (30%) infection. Fungal infection is associated with poor survival and death, thus requiring aggressive management. Thinning of temporal bone on CT, uncontrolled diabetes, severe hearing loss and facial paralysis score V/VI were associated with poor outcome of disease.

Key Words: Necroinflammatory otitis externa, *Pseudomonas aeruginosa*, Diabetes, Hearing loss, Facial paralysis, Temporal bone thinning, CT scan.

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INTRODUCTION

Necroinflammatory otitis externa (NOE) also known as malignant otitis externa (MOE) or skull-base osteitis (SBO) is a life-threatening infection of external auditory canal, *os temporalis* or base of skull, mostly seen in elderly and immunocompromised patients, particularly diabetics.^{1,2} Pathologically, it is divided into necrotizing otitis externa, in which only soft tissues and cartilage undergo necrosis, and osteomyelitis in which infection spreads to skull base bones and they undergo necrosis.^{3,4}

Pseudomonas aeruginosa, which is an encapsulated, gram-negative rod, is the most common organism known to cause NOE.⁵ Others, like *Staphylococcus aureus*, *Proteus mirabilis*, *Aspergillus fumigatus* and *Candida* species have also been implicated.⁶ Many factors affect the disease course and outcome of NOE, e.g. age, duration and control of diabetes mellitus, HbA1c levels, granulation tissue in external auditory canal, involvement of cranial nerves, and the intracranial extent of infection assessed radiologically. The typical clinical presentation is severe unremitting otalgia which gets worsen at night and is refractory to conventional analgesics.⁷ Other signs such as aural fullness, foul smelling otorrhoea and hearing loss may also be present. NOE can be vigorously treated with appropriate antibiotics, while surgery is reserved for diagnostic purpose and local debridement.⁸

The condition needs vigilance and evidence-based management guidelines in the local context. This study aimed to determine the association of gender, causative organisms, control of diabetes, and hearing loss with prognosis, measured in terms of six-month improvement of symptoms or expiry of patients presenting with NOE.

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METHODOLOGY

It was a retrospective cohort study conducted in the Department of ENT in collaboration with Pathology Department of King Edward Medical University/Mayo Hospital, Lahore over a period of about four years from 2016 to 2019. Patients with MOE/NOE were divided into two groups: One obligatory and other occasional (Table I). Presence of obligatory criteria was considered essential for diagnosis of NOE and inclusion in the study. Twenty-eight (28) patients fulfilled the essential obligatory (major) criteria of NOE and had complete clinicoradiological and pathological data, required for the study. Patients with only minor signs of NOE and insufficient information were excluded. All enrolled patients had been admitted in the ward and managed adequately. Data was collected retrospectively through medical records of ward, in a structured questionnaire proforma which included demographic details, clinical features, findings on computed tomographic (CT) scan imaging, audiological assessment, culture and sensitivity results of aural secretions, facial paralysis (House Brackmann Score⁷), histopathology reports of ear biopsies, treatment, co-morbidities and outcome. Incisional biopsy was taken in all patients for the purpose of diagnosis; however, surgical debridement was reserved for patients with extensive disease to skull-base and adjacent areas. Patients were followed up for a period of six months.

Table I: The diagnostic criteria of malignant otitis externa.

| Major (obligatory) signs |
|--|
| 1. Pain |
| 2. Exudate |
| 3. Edema |
| 4. Granulations |
| 5. Microabscesses |
| 6. Positive Technetium-99 (99Tc) scan of failure of local treatment after more than 1 week |
| 7. Minor (occasional) signs |
| 8. <i>Pseudomonas</i> |
| 9. Positive radiograph |
| 10. Diabetes mellitus |
| 11. Cranial nerve involvement |
| 12. Debilitating conditions |
| 13. Old age |

Data was analysed by using software, SPSS version 26. Quantitative measure, like age, was expressed in terms of mean and standard deviation. Qualitative data were expressed as frequency along with percentages. Pearson's Chi-square test was used to ascertain association between gender, clinico-radiological features, diabetic control, histopathological features, and prognosis of the disease, keeping p-value <0.05 as significant.

RESULTS

Twenty-eight patients fulfilled the inclusion criteria, in four years (2016-2019). Out of 28 patients, 17 were males (60.7%) and 11 females (39.3%). The mean age of presentation was 59.36 ±4.4 years. Association between gender and survival showed that 41.2% (7) males and 27.3% (3) females survived the disease; while 23.8% (04) males and one (9.1%) female expired within six months of diagnosis. In 11.8% (2) males and 27.3% (3) females, the disease remained static (p=0.340).

Thinning of temporal bone (2/5=40%) was common among the

expired patients. Other grave signs were sclerosis, erosion (mastoid bone), and inflammatory soft tissue in external auditory meatus (1/5=20% each). Nine out of 10 (90%) patients that showed inflammatory tissue only, showed improvement in symptoms (p=0.239). Lower motor neuron type facial paralysis of varying degree was seen in 17 (60.7%) patients (Table II). *Pseudomonas aeruginosa* was isolated in 14 (50%), *Staphylococcus aureus* in 7 (25%), fungus in 3 (10.7%) (*Aspergillus fumigatus*-2 (7.1%) and *Candida*-1 (3.6%)) species and no growth was isolated in 4 (14.3%) patients. Histopathology reports of ear biopsies showed granulation tissue in 24/28 (85.71%), nonspecific inflammation in 3/28 (10.7%), and squamous cell carcinoma in 1/28 (3.6%) cases. Association between biopsy reports and survival showed that 20% (1/5) patients diagnosed with squamous cell carcinoma and 80% (4/5) with granulation tissue (GT), expired within six months (p=0.543), while 90% (9/10) patients with GT and 10% (1/10) improved. Cultures of ear biopsies revealed that *Aspergillus* (2/5=40%) and *Pseudomonas* (1/5=20%) were commonest among the expired patients, while *staphylococcal* (6/10=60%) and *pseudomonal* (3/10=30%) infections were predominant among the improved patients (p=0.005). Association between hearing loss and survival revealed that 10/10 (100%) that improved had mild to moderate hearing loss (p <0.001). While 80% of the expired patients had (4/5) severe to profound hearing loss, and only 20% (1/5) had mild to moderate loss.

Twenty-four out of 28 (85.7%) patients were diabetics; and out of those 24, 18 (75%) had suboptimal control of disease with HbA1c levels of more than 7%. Other 4/28 (14.3%) had anemia, history of renal transplant and hepatitis C infection. Among expired group, 80% (4/5) had HbA1c of more than 7, and 20% (1/5) had good control of diabetes; while, 30% (3/10) of improved patients had HbA1c <7 and 70% (7/10) had uncontrolled diabetes (p=0.026. Table II).

DISCUSSION

NOE is a necrotising and destructive infection of the external auditory canal, temporal bone of skull base, and adjacent soft tissues. This study included 28 patients fulfilling the inclusion criteria and presenting in last four years (2016-2019). The gender and the mean age of presentation was similar to the findings by Musa, who found 60.9% males and 39.1% females with ratio of M/F 1.5:1.⁹ However, there was a marked difference of mean age and gender distribution in other studies.¹⁰

In this study, association between radiological diagnosis/CT findings and survival (six months) revealed that thinning of temporal bone was common among expired patients. Other grave signs were sclerosis, erosion (mastoid bone), and inflammatory soft tissue in external auditory meatus. Patients who showed inflammatory tissue only, showed marked improvement in symptoms. Skull-base osteomyelitis is a serious complication of NOE, which starts as a soft tissue (bacterial/fungal) infection in the EAC (external auditory canal). Then, it spreads through the Santorini fissures and the tympano-mastoid suture to the base of skull. As the disease progresses, it involves the jugular foramen and hypoglossal canal, which carries glossopharyngeal, vagus, spinal accessory, and hypoglossal nerves that also get involved in the spreading infection.¹¹

Table II: Association of gender, risk factors, facial paralysis, CT findings, biopsy, culture, hearing loss, and HbA1c with outcome and prognosis over a period of six months (Renal T: renal transplant, Staph: staphylococcus, Infl: inflammatory).

| Qualitative variables | | Improved n=10 | Static n=5 | Expired n=5 | Debridement n=4 | Lost to FU n=4 | Total n=28 |
|-----------------------------|-------------|------------------|---------------|----------------|--------------------|-------------------|---------------|
| | | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) |
| Gender p=0.340 | Males | 7 (70) | 2 (40) | 4 (80) | 1 (25) | 3 (75) | 17 (60.7) |
| | Females | 3 (30) | 3 (60) | 1 (20) | 3 (75) | 1 (25) | 11 (39.3) |
| Risk factors p=0.39 | Diabetes | 9 (90) | 5 (100) | 5 (100) | 1 (25) | 4 (100) | 24 (85.7) |
| | Anemia | 0 | 0 | 0 | 1 (25) | 0 | 1 (3.57) |
| | Renal T | 1 (10) | 0 | 0 | 0 | 0 | 1 (3.57) |
| | Hep C | 0 | 0 | 0 | 2 (50) | 0 | 2 (7.14) |
| Facial paralysis p=0.132 | Score II | 3 (30) | 2 (40) | 0 | 0 | 2 (50) | 7 (25) |
| | Score III | 1(10) | 2 (40) | 1 (20) | 1 (25) | 0 | 5 (17.9) |
| | Score IV | 0 | 0 | 2 (40) | 0 | 1 (25) | 3 (10.7) |
| | Score V | 0 | 0 | 1 (20) | 0 | 1 (25) | 2 (7.14) |
| | No FP | 6 (60) | 1 (20) | 1 (20) | 3 (75) | 0 | 11 (39.3) |
| CT findings p=0.239 | Infl. mass | 9 (90) | 3 (60) | 1 (20) | 4 (100) | 3 (75) | 20 (71.4) |
| | Thinning | 0 | 2 (40) | 2 (40) | 0 | 1 (25) | 5 (17.9) |
| | Sclerosis | 1 (10) | 0 | 1 (20) | 0 | 0 | 2 (7.14) |
| | Erosion | 0 | 0 | 1 (20) | 0 | 0 | 1 (3.57) |
| Biopsy report p=0.543 | Granulation | 9 (90) | 4 (80) | 4 (80) | 3 (75) | 4 (100) | 24 (85.7) |
| | Nonspecific | 1 (10) | 1 (20) | 0 | 1 (25) | 0 | 3 (10.7) |
| | Scc | 0 | 0 | 1 (20) | 0 | 0 | 1 (3.57) |
| Culture p=0.005 | Pseudomonas | 3 (30) | 5 (100) | 1 (20) | 4 (100) | 1 (25) | 14 (50) |
| | Staph. | 6 (60) | 0 | 0 | 0 | 1 (25) | 7 (25) |
| | Aspergillus | 0 | 0 | 2 (40) | 0 | 0 | 2 (7.14) |
| | Candida | 0 | 0 | 0 | 0 | 1 (25) | 1 (3.57) |
| | None | 1 (10) | 0 | 2 (40) | 0 | 1(25) | 4 (14.3) |
| Hearing loss p<0.001 | Mild to Mod | 10 (100) | 5 (100) | 1 (20) | 4 (100) | 4 (100) | 24 (85.7) |
| | Severe | 0 | 0 | 4 (80) | 0 | 0 | 4 (14.3) |
| HbA1c p=0.026 | <7 | 3 (30) | 0 | 1 (20) | 4 (100) | 2 (50) | 10 (35.7) |
| | >7 | 7 (70) | 5 (100) | 4 (80) | 0 | 2 (50) | 18 (64.3) |

The disease spreads to the centre and base of skull through four channels: external auditory canal, stylomastoid foramen, jugular foramen, and the apex of the petrous bone. CT and MRI findings are usually helpful in diagnosing NOE at admission, but do not specifically predict the outcome or survival of the disease.¹²

Association between biopsy reports and survival showed that 20% (5) patients diagnosed with squamous cell carcinoma and 80% with granulation tissue (GT) expired; while, 90% (9/10) patients with GT improved. *Aspergillus* (20%) and *Pseudomonas* (20%) were commonest among expired patients, while *Staphylococcal* (60%) and *Pseudomonal* (30%) infections were predominant among improved patients (p=0.005). This is in contrast with the findings by Musa, who reported complete improvement in 91% of infected patients (with *Klebsiella* and *Pseudomonas*).⁹ Many studies have shown that *Pseudomonas aeruginosa* is the most common microbiological organism isolated in culture specimens. Shavit *et al.* reported that *Pseudomonas aeruginosa* was the causative agent in 39 (44.3%) of 88 patients and *Staphylococcus aureus* in 7 (8%) patients.¹³ Bhat *et al.* found *Pseudomonas aeruginosa* in 11 (73%) of total 15 patients.⁸ Similarly, *Pseudomonas aeruginosa* was isolated

from 50% of 28 swab cultures of the external auditory canal pus. *S. aureus*, *A. fumigatus*, and *Candida* were identified in the rest of the patients.

Longstanding DM (diabetes mellitus) causes macrovascular and microvascular angiopathy, which results in suppressed microcirculation, decreased neutrophilic function, chemotaxis, adherence to endothelium, phagocytosis and microbicidal activity along with impaired cytokine production from macrophages.¹⁴ Macrovascular changes and atherosclerosis cause hypoperfusion, which markedly reduces the transport of antibiotics to the infected area and thus effectiveness of antibiotic therapy. Rigorous control of blood glucose levels and administration of multiple specific antibiotics are essential for treating NOE and preventing complications. In this study, 24 out of 28 (85.7%) patients were diabetics and out of those 24, 18 (75%) had suboptimal control of disease with HbA1c levels of more than 7%. Among the expired group, 80% (4/5) had HbA1c of more than 7 and 20% had good control of diabetes; while, 30% of the improved patients had HbA1c <7 and 70% (7/10) had uncontrolled Diabetes. This is similar to findings by Schwam, who observed uncomplicated diabetes in 42.1% and complicated diabetes in 17.8% cases.¹⁵ Although they also

stated that Diabetes is not independent risk factor for any outcome, which was not coherent with the present findings. Strict control of Diabetes is associated with better survival outcome and less hospital stay time.^{11,16}

In this study, those patients who improved, had mild to moderate hearing loss; while, 80% of the expired patients had severe to profound hearing loss and only 20% had mild to moderate loss. Other studies did not find any improvement in hearing loss after treatment.¹⁹ This could be due to lesser number of patients observed than in this study. Mardassi observed improvement in facial paralysis and hearing loss in 75% cases after administering hyperbaric oxygen therapy and recurrence occurred in 14.28% of cases¹⁷

Since NOE is not specifically a surgical disease, incisional biopsy is done to obtain adequate pus cultures, debridement of necrotic/dead tissue, or to rule out presence of an underlying malignant neoplasm⁵. Surgical debridement is considered only an option, if medical management fails to treat infection.¹⁸ NOE had a significant mortality rate, approximately up to 50% by some authors.^{11,12} Disease outcome has improved markedly after the introduction of quinolones for NOE, like ciprofloxacin and other antipseudomonal agents, in the early 1990's². Only early and effective treatment can result in improved prognosis, reduced neurological involvement, and decreased mortality.¹⁹ In this study, surgical debridement was done in 14.3% patients. After administering specific therapy, 35.7% patients improved and were discharged, 17.85% patients expired, or showed no improvement, in symptomatology despite adequate management of the disease. The rest (14.3%) were lost to follow-up.

Mortality in NOE is associated with multiple risk factors like immunosuppression (anemia, transplants, hepatitis C, diabetes), local invasion of meninges or brain parenchyma, vascular involvement of carotid arteries resulting in ischemic thromboembolic stroke and aneurysm.²⁰ In this study, all the three patients who had anemia and hepatitis C infection expired. However, patients' with renal transplant and immunosuppression improved after treatment (Table II). Similarly, 60% with advanced cranial nerve involvement expired. Thus, indicating the aggressiveness of the disease after cranial involvement.

CONCLUSION

This study showed a rising community-acquired NOE with *Staphylococcus aureus* and less with *Pseudomonas* infection than previously reported. Fungal infection is associated with poor survival and death, thus requiring aggressive management. Optimal control of Diabetes is the main factor in disease progression to skull-base and other complications. Thinning or sclerosis of temporal bone on CT, uncontrolled Diabetes, severe hearing loss, and facial paralysis score V/VI, are associated with adverse outcome.

ETHICAL APPROVAL:

Study was approved by Institutional review board of King Edward Medical University, Lahore, Pakistan (approval letter

number: 68/RC/KEMU, dated 16/01/2020).

PATIENTS' CONSENT:

Since this study was retrospective, consent was not taken.

CONFLICT OF INTEREST:

Authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:

KC: Data interpretation.

NA: Critical review.

NR: Manuscript writing.

SQ: Data collection.

SA: Data analysis.

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