Increasing burden of necrotizing otitis externa: our experience of 38 cases

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ABSTRACT

Background: Necrotizing otitis externa is an infection affecting immune-compromised and elderly diabetic patients resulting in complications with significant morbidity and mortality. We present our experience with this disease, along with the investigative tools and treatment modalities that benefitted most. The objective being to analyze the course of the disease and the benefit of having an institutional protocol for its management.

Methods: This is a retrospective observational study on patients diagnosed with necrotizing otitis externa between 2013-2019.

Results: Out of 38 patients 36 were diabetics, the commonest clinical presentation included otalgia in 37 patients, granulations in 35, facial nerve palsy in 14 and Pseudomonas aeruginosa was isolated in 19 patients. They were managed with multidrug combination antibiotic therapy, topical dressing and drops with 27 showing improvement.

Conclusions: We recommend a diagnostic triad for NOE comprising of otalgia in an elderly diabetic patient with granulations in the external auditory canal. It is best managed by controlling diabetes, appropriate antibiotic combination, topical dressing, and sometimes surgical debridement.

Keywords: Malignant otitis externa, Skull base osteomyelitis, Ciprofloxacin, Ceftazidime, Pseudomonas

INTRODUCTION

Necrotizing otitis externa (NOE) or malignant otitis externa, is a disease described by Chandler as a life-threatening, progressive bacterial infection of the external auditory canal (EAC), mastoid and skull base, commonly occurring in elderly diabetics or immune-compromised patients.1 Though a case of NOE was first reported in 1838 by Toulmouche, its detailed description as a distinct clinical entity was in 1968 by Chandler. He termed it ‘malignant’ due to its aggression, spread, complications and resultant morbidity and mortality.1

Outcome improvement has led to suggestions that the term malignant should be abandoned, as it is non-neoplastic. Terms like ‘necrotizing external otitis’ used for aggressive soft tissue infection without the involvement of bone and ‘skull base osteomyelitis’ when bone was infected generate more confusion. For uniformity, we will use the term NOE.2-3 Studies show NOE has a mortality of 23% with no deep structures involved, 67% if facial nerve is involved and 80% if deep cranial nerve/ jugular vein is involved4. Increasing prevalence of diabetes and human immunodeficiency virus (HIV) has increased the incidence of NOE.5

Awareness of NOE can help detect these patients earlier and improve outcomes. Diagnosis is made on the basis of clinical history and findings often supported by a positive technetium 99 m (methylene diphosphonate) bone scan. Cohen et al published diagnostic criteria for NOE (Table 1).6 All obligatory criteria must be present for a diagnosis. A Te99m scan is beneficial, but when
unavailable, failure to respond to 1-3 weeks of local treatment assists diagnosis.\textsuperscript{5}

**Table 1: Criteria for diagnosis of NOE.\textsuperscript{6}**

| The major (obligatory) signs | The minor (occasional) signs |
|-----------------------------|-----------------------------|
| Pain                        | Pseudomonas                 |
| Exudates                    | Positive radiograph         |
| Edema                       | Diabetes mellitus           |
| Granulations                | Cranial nerve involvement   |
| Micro-abscesses when surgery is done | Debilitating condition |
| Positive Tc99 scan or failure of local treatment after more than 1 week | Old age |

Immuno-compromised patients are at increased risk of NOE. It also affects non-diabetics, young diabetics, patients on cytotoxic drugs and infants.\textsuperscript{7,12} Elderly diabetics are prone due to macroangiopathy (atherosclerosis) and microangiopathy, resulting in poor local blood supply, compromising systemic antibiotic uptake. Their immune response is compromised by poor migration, reduced chemotaxis and defective phagocytosis of polymorphonuclear leucocytes; this decreases host response to Pseudomonas.\textsuperscript{13,14} Their cerumen has a higher pH, which is a hospitable environment for bacteria.\textsuperscript{15}

*Pseudomonas aeruginosa* is the most common pathogen, seen in up to 95% cases in some studies.\textsuperscript{7,14,16} *Aspergillus* is also seen, often beginning in the middle ear/mastoid instead of the EAC.\textsuperscript{17} Other organisms like *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Proteus* and *Salmonella* are also reported.\textsuperscript{18} Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels are non-specific measures of inflammation that are raised in cases of NOE prior to treatment and can be used as measures of treatment response. An ESR of over 100 mm/hour has been seen in NOE.\textsuperscript{19}

A technetium-99m scan is useful in diagnosis as it is positive early in NOE. Serial gallium-67 citrate scans evaluate treatment response as uptake of gallium decreases with disease control.\textsuperscript{20,21} A high resolution computed tomography (HRCT) scan of the temporal bone is useful as an initial investigation when these are unavailable.

NOE spreads via the fissures of santonini, osseo-cartilaginous junctions to involve the temporal bone and adjacent structures progressing to osteomyelitis and other complications.\textsuperscript{7} Bone destruction can occur in the skull base, temporomandibular joint and mastoid that sometimes extends into the petrous apex, jugular foramen and carotid canal. Advanced cases develop bony sequestration, abscess formation, and soft tissue edema in the parapharyngeal space and nasopharynx.\textsuperscript{22} Treatment of NOE involves local antibiotics and debridement, systemic anti-pseudomonal antibiotics, surgical debridement and where available, hyperbaric oxygen as adjuvant therapy for refractory cases.\textsuperscript{22-28}

Current investigation details the clinical profile and management protocol followed for 38 cases diagnosed with NOE from January 2013 to September 2019. The objective of current study is to analyze the course of NOE and look for benefits if any of having an established protocol based on clinical parameters to diagnose and treat NOE in otolaryngologic practice hoping to minimize confusion and improving outcomes.\textsuperscript{5}

**METHODS**

Current study was a retrospective observational study conducted on 38 patients in a tertiary care institute. Data was compiled from records of patients admitted between January 2013 and September 2019. All were managed on an inpatient basis after coming to a provisional diagnosis, and once treatment was complete underwent routine outpatient follow up.

When seen in the outpatient clinic, a provisional diagnosis of NOE was made based on otalgia for more than 10 days despite receiving treatment (topical antibiotic drops and/or systemic antibiotics and/or analgesics and/or topical dressing); granulations/edema in EAC, diabetes/any immunocompromised state, aural swab showing *P aeruginosa* or *S aureus*, an HRCT scan of temporal bone showing soft tissue changes and bone erosions in EAC, with extension along the skull base and adjacent structures.

All patients with a proven diagnosis of NOE were included in the study based on clinical, pathologic and radiologic findings and admitted and followed up for at least six months after discharge were included in the study. Patients who did not follow up were excluded. No specific sampling technique was used. There are several staging systems, mostly employing a technetium 99m scan, which was unavailable to us. Hence, we adopted a system using clinical, radiological and clinicoradiological findings and categorized patients into: Stage I: clinical evidence of soft tissue infection of the EAC and beyond, without bone erosion on HRCT scan of the temporal bone. Stage II: the above features with bone erosion. Stage III: the above features with cranial neuropathy. Stage IIIa: when associated with facial (VIIth cranial) nerve involvement and stage IIIb with multiple cranial nerve involvement. Stage IV: the above (stages I, II and III) features with meningitis, empyema, sigmoid sinus thrombosis or brain abscess.\textsuperscript{7} This is a modified version of the staging system.\textsuperscript{29}

Patients were then admitted and started on multidi drug combination therapy with ceftazidime 1 gm IV 12 hourly and oral ciprofloxacin 750 mg unless prior aural swabs...
revealed different sensitivity or renal impairment required dose adjustment. They underwent routine blood investigations including a complete hemogram with ESR, CRP, renal function tests, liver function tests, an aural swab, fasting blood sugar level, post prandial blood sugar level and glycosylated hemoglobin (HbA1C); with ESR and CRP done weekly to monitor progress. They were treated with 21 days of parenteral antibiotics and daily insertion of medicated (polymyxin B and neomycin sulphates ointment with beclomethasone or mupirocin with beclomethasone) wicks and topical drops of polymyxin B, neomycin or ciprofloxacin or ofloxacin placed over the wick thrice a day.

Patients were monitored daily using a visual analogue scale (VAS) for otalgia, and analgesics were routinely prescribed (intravenous or oral acetaminophen or opioids); they were tapered as per reduction in VAS scores. Similarly, daily random blood sugar levels (RBSLs) were done eight hourly in diabetics. These patients received a combination of rapid and intermediate acting insulins on a fixed scale, which was decided by an endocrinologist. All patients underwent HRCT scanning and subsequently Otomicroscopy and de-bulking of any granulations which were sent for histopathology. Surgical intervention was considered in patients with persistent otalgia for more than 10 days (VAS score of more than 50%), persistent granulations with or without facial nerve palsy and worsening of clinical picture (such as development of facial palsy or involvement of the skull base) despite using parenteral antibiotics. Patients were discharged after receiving adequate dose of parenteral antibiotics for 3-6 weeks, resolution of otalgia, granulations and control of diabetes. All patients were prescribed oral ciprofloxacin 750 mg twice a day for 8-10 weeks with topical drops and followed up for 4-6 months. Available sample was then compiled in a spreadsheet using Microsoft Excel, with no other specific statistical software utilized, and data was analyzed and presented as simple percentages.

RESULTS

The study included 38 patients, 31 (82.3%) of these were male and 7 (17.7%) were female (a male to female ratio of 4.4 to 1). Patients were aged between 48 and 86 years with an average age of 59.89 years. All patients were diabetic with the exception of one patient who suffered from chronic kidney disease (CKD) and was on routine dialysis and another who had HIV. The average HbA1c at admission was around 8.7 g/dl suggesting poor glycemic control. In addition, 13 (34.21%) patients also had concomitant hypertension while 4 patients had end stage renal disease (10.52%). The average hospital stay of patients was 23.57 days (ranging from 8 days to 64 days). The commonest presenting complaint was pain in the affected ear and the surrounding area, seen in 35 patients (92.01%), followed by ear discharge seen in 28 (73.68%) patients, the remainder presenting with canal wall oedema (2) and unilateral headache (1). Amongst complications, 14 (37%) had facial palsy, and 3 (7%) had multiple cranial nerve involvement. Two patients had preauricular swelling due to infiltration of the temporomandibular joint with one of them developing a discharging sinus (Figure 1). One patient developed a mastoido-cutaneous fistula post aggressive surgical debridement (Figure 2).

Figure 1: Extension of disease to temporomandibular joint with formation of a chronically discharging sinus with purulent discharge (white arrow: sinus).

Figure 2: Mastoid cutaneous fistula.

Figure 3: HRCT temporal bone of a patient with skull base osteomyelitis extending to petrous apex (white arrow: osteomyelitic changes).
**Bacteriology**

*P. aeruginosa* was seen in 19 patients (50%) followed by coagulase negative *Staphylococcus aureus* in 5 patients (13.17%) and *Klebsiella species* in 2 patients. The cultures of 4 patients were sterile. Laboratory contaminants (*Acinetobacter baumanii, non-albicans Candida*) and mixed flora were isolated in 4 cultures. All pseudomonas isolates were sensitive to third generation cephalosporins (ceftazidime, cefoperazone with sulbactam, and ceftriaxone) and ciprofloxacin. Some isolates of Pseudomonas showed sensitivity to meropenem and vancomycin which were used in non-responders.

**Staging**

Based on the aforementioned staging method, 25 patients were categorized as stage I and II (65.78%). 6 patients were stage IIIa (15.78%), 3 were stage IIIb (7.89%) and 4 were stage IV (10.52%).

**Radiology**

The commonest finding was presence of soft tissue and bony erosion in the EAC. There were 3 cases that showed extension to petrous apex, cranial cavity and contralateral petrous apex (Figure 4). Patients with stage III and IV underwent magnetic resonance imaging (MRI) for detailed intracranial evaluation.

**Treatment**

All patients were started on ceftazidime 1 g IV 12 hourly and ciprofloxacin 750 mg BD (doses adjusted as per renal function) unless culture showed resistance and an alternate sensitivity pattern. Of the 38 patients, 25 (65.78%) received ceftazidime, 5 (13.17%) received ceftriaxone and 3 (7.89%) received cefoperazone with sulbactam and 5 received piperacillin with tazobactam. Some isolates of Pseudomonas were also showing sensitivity to meropenem and vancomycin which were used in non-responders after a long period (4 weeks) of cephalosporin usage in 2 patients. The course of parenteral antibiotics lasted for a mean of 24 days (3-61 days). Oral ciprofloxacin was given to all patients for a mean duration of 6 weeks (3-42 weeks) following discharge from hospital (dosage 750 mg BD with adjustment as per renal function). A single patient non-responsive to multi-drug antibacterial therapy was empirically started on oral voriconazole 200 mg BD for 3 weeks on suspicion of fungal etiology and he responded well. Thus, 16 (42%) patients received purely medical therapy with parenteral antibiotics, ear drops and daily wick placement, while 19 (50%) underwent debridement of granulations in one or more sittings under local anaesthesia with the assistance of otomicroscopy. This would also be followed by wick placement. A single patient underwent mastoidectomy with tip resection and debridement of granulation tissue. It was not possible to intervene surgically in 2 patients due to multiple co-morbidities and anaesthesia fitness though they were planned for the same in view of poor response to conservative measures (including sepsis, meningitis and CKD).

**Outcomes**

Total 27 (71%) patients improved with the above protocol, 6 patients died of which 4 were thought to be as a result of disease complications with disease specific mortality of 10.52%, 3 were lost to follow up and 3 (7.89%) did not show resolution but survived with the disease with appropriate management of pain. Prognosis is good in stage I and II and worsens progressively with extensive disease or in the presence of complications. 4 deaths were due to complications related to NOE such as meningitis and sepsis (Table 2).

**Table 2: Summary of observations.**

| Parameters            | N (%)       |
|-----------------------|-------------|
| Age (years)           | Range 48 to 80 |
|                       | Average 59.89 |
| Gender                | Male 31 (81.5) |
|                       | Female 7 (18.42) |
|                       | Ratio 4.4:1 |
| Clinical features     | Diabetics 36 (94.73) |
|                       | Otorrhea 37 (97.36) |
|                       | Otorrhea 28 (73.68) |
|                       | Granulations in EAC: 35 (92.10) |
|                       | Cranial N palsy facial 13 (34.2) |
|                       | Other complications 5 (13.15) |
| Organisms             | *P. aeruginosa* 19 (50) |
|                       | *S. aureus* 5 (13.17) |
| Mortality             | 4 (10.52) |
| Improvement           | 27 (71) |
Table 3: Association between diabetes, otalgia and granulation tissue in the external auditory canal in various studies.

| Reference        | N   | Otalgia (%) | DM (%) | Granulations (%) |
|------------------|-----|-------------|--------|------------------|
| Holten et al\(^5\) | 25  | 100         | 100    | 100              |
| Loh et al\(^9\)   | 22  | 73.7        | 94.70  | -                |
| Hariga et al\(^3\) | 19  | 94.7        | 94.7   | 52.6             |
| Soheilipour et al\(^3\) | 18  | 100         | -      | 77.77            |
| Lambor et al\(^3\) | 27  | 100         | 84.6   | 92.6             |

Table 4: Mortality of NOE as reported in other management protocols.

| Reference         | Mortality (%) |
|-------------------|---------------|
| Chandler et al\(^8\) | 32            |
| Loh et al\(^9\)   | 21            |
| Hariga et al\(^3\) | 10.2          |
| Lucente et al\(^2\) | 25            |
| Lambor et al\(^3\) | 14            |

DISCUSSION

NOE is usually seen in elderly patients (though the youngest age it has been reported is 10 months).\(^8\) Patients in our study were between 48 and 86 years with the average age being 59.89 years. Other studies report a similar range, possibly explained by a diminished host response to infection in the elderly.\(^1,6,19\) It is also seen more often in males: with 81.57% of our patients being male, the reasons for which are unknown.

Another characteristic is its near constant association with uncontrolled diabetes: 94.73% of our cases had diabetes in most of whom it was uncontrolled, as revealed by raised glycosylated hemoglobin levels. The average level of HbA1C was 8.7 gm%. HbA1c levels of 4-6 gm% were considered non-diabetic and 6-8 gm% as controlled diabetes.

The role of diabetes in NOE is attributed to microangiopathy, which causes ischemia followed by degeneration of cartilage and dermis in the EAC, and along with this impairs healing capacity and allows progression. Patients with good glycemic control presented at stage I or II of the disorder, and fared better than those with poor glycemic control who were in stage III or IV. An endocrinologist managed diet and insulin dosage and helped achieve adequate glycemic control in our patients. Two patients in our series were non-diabetic; however, suffered from HIV and CKD. The exact cause of necrotizing otitis externa in non-diabetics is unknown, but it could be associated with age-related small vessel disease and altered immune function.\(^7-9\)

**Clinical features**

NOE presents as otalgia, otorrhoea and granulation in the EAC. The otalgia is a deep, boring, nocturnal (often causing sleep disturbance) pain resistant to analgesics.\(^3\) In literature, otalgia has an incidence of 75-100% in NOE.\(^1,6,31,34\) Current case series also had 37 (97.3%) cases with otalgia. Otorrhoea was the next commonest symptom seen in 73.68%. One patient did not have otalgia but presented with deep seated headache, in whom a possible fungal etiology of NOE was suspected radiologically (imaging showed petrous apex and clival involvement with intravascular thrombosis of the related segment of internal carotid artery) but could not be proven with appropriate staining or culture.

The commonest finding was granulation tissue in the EAC, similar to previous reports.\(^5,6,32,35,36\) The granulation tissue and edema can narrow the EAC lumen.\(^5,6,38,39\) The tympanic membrane is usually normal. Granulations should undergo histopathological studies to rule out malignancy, histiocytosis, tuberculosis etc. Granulations were present in 35 cases (92.10%). Hearing loss was observed in the majority of the cases; conductive hearing loss can be due to EAC obstruction by granulation or edema, while sensorineural hearing loss can be due to ageing or diabetes mellitus. The association between diabetes, otalgia and granulation may be seen in several studies as seen in (Table 3).

**Investigations**

*Pseudomonas aeruginosa* was the commonest isolate, seen in 19 patients (50%). It opportunistically affects patients with a defective immune system. *Pseudomonas* is a Gram-negative obligate aerobe that can cause selective vasculitis. It invades the arterial, capillary or venous walls, and causes focal coagulation necrosis. These actions are due to endotoxins, exotoxins, enzymes (haemolysins, lecithinases, lipases, esterases and proteases) and neurotoxins that may play a role in cranial neuropathy.\(^40\) There is a strain that produces a mucoid layer which protects against phagocytosis and antibiotic action. The second most common organism isolated was *S aureus* (coagulate negative) seen in 13.17% cases, similar to previous papers.\(^27,32\) In contrast to prior reports of *Aspergillus fumigatus*, current study failed to find a fungal culture positive. However, there was a patient who presented without otalgia but had deep seated headache and responded well to antifungals (oral voriconazole). His swabs were negative and he did not show clinical response to initial antibacterial therapy indicating that awareness of fungal etiology is necessary. All pseudomonas isolates in our study were sensitive to ciprofloxacin (fluoroquinolones), third generation cephalosporins like ceftazidime, ceftriaxone and cefoperazone, which is in contrast to reports of emerging
resistance to fluoroquinolones. Most of the other organisms isolated, including Staphylococcus aureus, klebsiella species and enterococci, were also sensitive to these antibiotics.

HRCT scan defines anatomical extent of the osteomyelitic process. It is limited by its inability to detect bone erosions in early stages of disease. They can detect disease when 30-50% of bone erosion has occurred, such as erosion in the canal and petrous apex (Figure 1). Magnetic resonance imaging evaluates intracranial extension e.g. a patient had numerous abscesses along the eustachian tube and prevertebral musculature which were not detected on prior HRCT, indicating the importance of advanced imaging in managing NOE. Radionuclide scans using technetium-99m methylene diphosphonate or gallium-67 citrate, can detect disease early. Radionuclides accumulate at sites of osteoblastic activity, and can detect up to 10% osteogenic activity. Indium (In111) labelled leukocyte scans are more specific to inflammatory processes and may be better than gallium citrate Ga 67 scans in assessing disease resolution.

Staging

Staging facilitates understanding current disease status, communication between surgeons and aids management and prognosis. Current staging system from a prior study is easy to implement in clinical practice as it relies on clinical history, and CT scan findings which are far more easily available.

Treatment modalities

There is no consensus on the therapeutic approach in NOE. Aural toilet along with a swab of any pus or exudate from the EAC should be taken before placing any medication. Granulation and pain control depend on local treatment including regular insertion of medicated wicks or topical ear drops. The role of topical antibiotics is control depend on local medication. Granulation and pain control depend on local treatment including regular insertion of medicated wicks, serial debulking and topical medicated wicks, serial debulking of the EAC undergo otomicroscopy and biopsy of granulation. In cases refractory to aggressive antibiotics and topical medicated wicks, serial debulking was done under local anesthesia. A single patient with grade IV disease underwent aggressive debridement of necrotic bone with amputation of mastoid tip, surrounding bone and soft tissues and developed a mastoido-cutaneous fistula in the process of healing. This improved disease control and the patient survived for two years. Later imaging revealed progress of disease to petrous apex and adjacent tissues and subsequently the patient deteriorated.

Hyperbaric oxygen therapy is often used in centers with access to hyperbaric chambers. It improves oxygen tension in inflamed tissue, promotes bacterial destruction by polymorphonuclear leucocytes, stimulates vascular proliferation and osteoblastic and osteoclastic activity which facilitates faster woundhealing. Studies have claimed beneficial effects but there is no prospective data. It is limited by availability. Cranial nerve palsy is a commonly seen complication in NOE, indicating advanced disease and raising mortality to 80% in some studies. The facial nerve is most commonly affected, with some reports of up to 60%. Facial nerve paralysis was observed in 14 (37%) cases. Other cranial nerves involved are IX, X, XI. Paralysis of cranial nerves VI and XII is rare, but reported. Involvement of cranial nerve VI was seen in 2 patients, probably following involvement of the petrous apex. Subsequent disease progression involves the clivus, contralateral temporal bone, sphenoid, carotid artery, temporomandibular joint, parapharyngeal space, central venous sinuses, extradural space and meninges. Temporomandibular joint involvement was seen in 3 (7.89%) cases, and managed conservatively with analgesia and aggressive antibacterial therapy. Infective thrombophlebitis or thrombosis of the internal carotid artery can be terminal. 2 patients developed infective thrombophlebitis thought to be due to skull base osteomyelitis, despite minimal otalgia, ear discharge and no granulation.
Outcomes and survival

In our series mortality was 10.52%, lower than that reported in literature.22 As these patients are elderly and have comorbidities, death is associated with illnesses such as CKD or ischemic heart disease. In 4 patients, death was from complications of NOE while at advanced stages of the disease.

There were no prospective/randomized control trials comparing results and courses of management. Retrospective reviews show that use of anti-pseudomonal antibiotics has improved outcomes, reduced need of surgery and increased survival (Table 4).

CONCLUSION

It can be concluded that an elderly diabetic with otalgia and granulations in the EAC should be considered a diagnostic triad for NOE. This with isolates of Pseudomonas aeruginosa constitutes the most important parameters for diagnosis. HRCT scan can assess the extent of disease, but cannot replace scintigraphy studies. Combination therapy with third generation cephalosporins and fluoroquinolones is the mainstay of treatment, supplemented by surgical debridement in those with granulations. Control of diabetes with endocrine referral also assists in improving outcome. Subsequently reduction in pain on a VAS, control of diabetes and resolution of granulations are signs of clinical improvement. A large-scale prospective analysis is needed to establish guidelines, limit delayed/missed diagnoses, reduce morbidity, mortality and improve outcomes.

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