

NECROTIZING OTITIS EXTERNA: CURRENT KNOWLEDGE AND DILEMMAS IN MANAGEMENT

Peled Chilaf MD¹, Kraus Mordechai MD¹, Kaplan Daniel MD¹

¹Department of Otolaryngology- Head and Neck Surgery, Soroka University Medical Center and the Faculty of Health Sciences, Ben Gurion University, Beer Sheva, Israel.

Corresponding Author: Peled Chilaf, Department of Otolaryngology- Head and Neck Surgery, Soroka University Medical Center and the Faculty of Health Sciences, Ben Gurion University, Beer Sheva, Israel. Tel: (+) 972-8-6400635, Email: chilafp@gmail.com

ABSTRACT

Abstract: Necrotizing otitis externa (NOE) is a severe inflammatory process of the external ear and temporal bone. Although there are dozens of publications dealing with this serious condition, there are still fundamental issues not fully understood in the diagnosis and treatment of NOE. The aim of this review is to describe the current approach to the management of NOE and emphasize the main issues which lack data and need to be further evaluated.

Materials & methods: We used Pub Med/MEDLINE to search for review articles in English using key words “necrotizing otitis externa”, “malignant otitis externa”, “necrosis”, “otitis externa”.

Conclusion: With increasing antibiotic resistance rates, isolating the pathogen and gaining an antibiotic profile are of the utmost importance. Non-Pseudomonas A. NOE and mycotic NOE pose special treatment dilemma, and further data is required for establishing appropriate guidelines. The role of surgery is still unclear but seems to have a place in refractory and/or culture negative cases. Follow up for patients with NOE may be performed with the help of periodic nuclear imaging or with periodic measurements of inflammatory markers.

INTRODUCTION

Necrotizing otitis externa (NOE), also known as malignant otitis externa is an inflammatory disorder involving the external ear and temporal bone. Left untreated, this severe inflammatory process may have grave consequences. NOE was first described by Chandler in 1968 [1] and although there have been dozens of reports on the subject since, there are still fundamental issues not fully understood in its diagnosis and treatment. The aim of this review is to describe the current approach to the management of NOE and emphasize the main issues which lack data and need to be further evaluated.

Presenting symptoms

NOE is a continuum of otitis externa, and as such, it represents a wide array of clinical conditions. As a result, there is no true consensus regarding the distinction between severe otitis externa and NOE, nor are there clear diagnostic criteria for NOE. Chandler¹ first described NOE as a severe inflammation of the external ear invading soft tissue, cartilage and bone occurring among elderly diabetic patients. Cohen and Friedman [2] suggested a diagnostic criterion for NOE, classifying the presenting symptoms as obligatory (pain, edema, exudate, granulations, microabscess, positive bone scan or failure of local treatment >1 week and pseudomonas in culture) and occasional (diabetes, cranial nerve involvement, positive radiograph, debilitating condition and old age). Hollis et al [3], a generation later, based the diagnosis of NOE on clinical findings (granulation tissue arising from the external auditory canal) raised serum inflammatory markers and radiographic evidence of soft tissue (with or without bone erosion) in the external auditory canal and infratemporal fossa. Other parameters used for the diagnosis of NOE include age [4] and necrosis shown in histopathology [5].

Several differences in the presentation of NOE among patients with different underlying conditions have been described. HIV patients with NOE were reported to be younger, and in some cases did not present the classic aural polyps or granulation tissue [6]. Additionally, Fungal NOE has been reported to be more common among HIV patients [7]. NOE in children has a more acute onset compared to adults, with a more pronounced systemic effects such as fever, malaise and leukocytosis [8]. Some NOE patients may present with facial nerve palsy or other cranial nerve involvement. Although these may relate to extensive bone involvement- a progressive form of disease, it doesn't necessarily indicate a worse prognosis [9].

Bacteriology

Pseudomonas Aeruginosa (PSA) is the most common causative agents for the development of NOE [3, 10, 11]. PSA is a gram-negative facultative anaerobe coccobacillus bacterium. It may be found in the soil or water and it thrives on moist surfaces. PSA is rarely a member of the normal flora of the external ear [10, 12]. The bacteria usually colonize the external ear following exposure to moist environment and penetrate the skin after local trauma. Virulent factors include lytic enzymes such as collagenase, elastase and others which cause local vasculitis and endarteritis further assisting in the penetration to the surrounding soft tissue. Resistance of PSA to antibiotics arises from mutations on target enzymes and formation of biofilm [13]. The prevalence of PSA NOE has been reported to decline in recent years and, at the same time, reports of culture negative NOE has been inclining [11]. Since most of the patients with NOE received local and/or systemic anti PSA antibiotics prior to hospitalization, these shifts raise concern regarding bacterial resistance. Several other organisms such as *Staphylococcus aureus* [14], *Klebsiella* species [15], *Streptococcus epidermidis* [16] and others were reported to cause NOE. These cases are rare and it is unclear whether they represent true pathogens [3].

Fungal pathogens have also been known to cause NOE. Among them, *Aspergillus* species has been reported to be the most common pathogen [3] followed by *Candida* species [17]. Although less common than PSA, these pathogens should be considered in refractory cases, especially in cases where initial improvement under antibiotic treatment is seen followed by clinical deterioration, as well as in non-diabetic patients. A positive fungal

culture taken from the external ear canal poses a dilemma for the treating physician. Since many patients are treated with steroids containing local ear drops prior to hospitalization it is unclear whether the isolated fungi are the true offending agent or a secondary infection due to the local steroid treatment. From this reason the decision of initiating anti-fungal treatment is, in many cases, delayed. Gruber et al [18] reported the use of polymerase chain reaction (PCR) in deep tissue biopsies in three culture negative refractory cases. In all patients' fungal pathogens were isolated, which may indicate a higher rate of fungal NOE than previously reported. It appears that deep tissue cultures may have a role in the evaluation and treatment of NOE patients. The exact indications and timing however, are still no clear.

Diagnostic Imaging

Current imaging studies used in the diagnosis of NOE include computer tomography (CT), magnetic resonance imaging (MRI) and nuclear imaging.

CT is the most common initial imaging modality. With the use of high resolution CT of the temporal bone (TB-HRCT), bone changes may be seen in the temporomandibular joint (TMJ), temporal bone and skull base (figure-1). It is important to emphasize that these changes are evident only when demineralization of bone reaches at least 30%. Furthermore, other conditions may cause cortical erosions of the temporal bone such as tumors, middle ear cholesteatoma and keratosis obturans, thus CT lacks the sensitivity and specificity for the diagnosis and follow up of NOE. On the other hand, involvement of the middle ear, mastoid and nasopharynx on initial CT have been shown to carry a worse prognosis among NOE patients [19, 20]. Regardless, the high availability of CT scan helps the physician in assessing disease extent during initial evaluation and for excluding other pathologies such as cholesteatoma, foreign body with soft tissue reaction and malignancy.

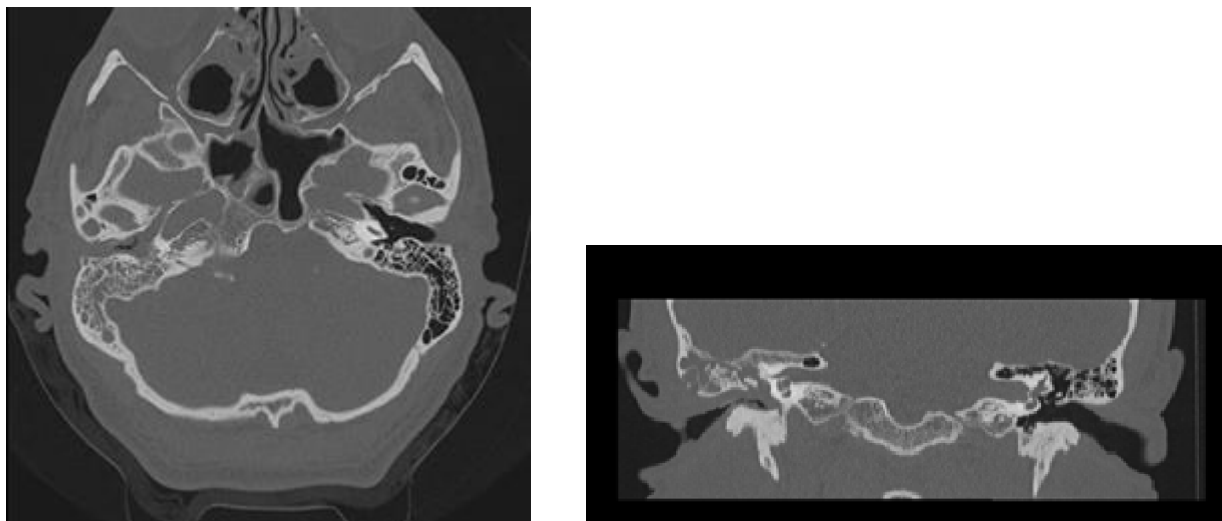


Figure 1: High resolution CT in (axial and coronal) in a patient with a right sided NOE. Cortical bone erosions and soft tissue fullness in the external ear canal, middle ear and mastoid air spaces are seen.

MRI is superior to CT in the evaluation of soft tissue, in particular the parotid, meninges, cranial nerves and medullary bone spaces [21]. Changes in medullary bone and soft tissue are seen on MRI as late as 12 months after initiation of treatment, limiting MRI's suitability to assess disease progression [22].

Nuclear imaging used in the diagnosis of NOE includes technetium-99, gallium-67 and indium-111. Technetium-99 accumulates in bone and reflects osteoblastic activity. It is relatively inexpensive and has a high sensitivity in the evaluation of bone involvement. Since these bone changes continue also after the inflammatory process has ended, it is not suitable for assessment of disease resolution.

Gallium-67, an isotope absorbed by macrophages and reticular endothelial cells, is a sensitive tool for the evaluation of inflammatory processes (figure-2). It accumulates in any area of active inflammation (soft tissue and bone), thus for the diagnosis of osteomyelitis both Technetium-99 and Gallium-67 measurements are required. The main disadvantage of Gallium-67 scan is poor anatomical localization, requiring SPECT/CT imaging to increase anatomical accuracy [21]. Gallium-67 absorption rapidly resolves after the inflammatory process has ended and as a result it is considered by many to be the most sensitive tool for the evaluation of disease progression and treatment response. Although sensitive, there have been reports of false negative results in cases where planar Gallium-67 imaging was used [23], as well as in cases of recurrent NOE [24]. Indium-111 labelled white blood cell scan has also been used in the diagnosis of NOE. As part of the ongoing inflammatory process, white blood cell migration occurs, causing accumulation of the labeled cells in the inflamed areas. Although considered as sensitive as Gallium-67 scan in the setting of acute inflammation, its sensitivity decreases in longstanding-chronic infections (due to decreased white blood cell migration).



Figure 2: sagittal, coronal and axial Gallium-67 scan showing increased uptake in the left ear consistent with the diagnosis of NOE.

Treatment

The most common first line systemic antibiotics given for PSA NOE include quinolones and ceftazidime (reported susceptibility rates in the USA of 68% and 80%, respectively [25]). Other regimens include the addition of rifampin, aminoglycosides and others. Since NOE is considered as osteomyelitis, recommended treatment duration is 6 weeks although larger variations exist in the literature (from 12 days to 15 weeks). Local treatment includes aminoglycosides or quinolone-based ear drops (similar to the treatment for acute otitis externa), however their exact role in the treatment of NOE is not clear.

Cases of ciprofloxacin resistant PSA have increased in recent years [26] with a reported incidence ranging between 31%-37.5% among NOE patients [27-29]. One reason for this might be due to prolonged and improper use of local quinolone-based ear drops at the initial stage by the primary care physician. It is of vital importance that high-risk patients (mostly elderly with DM and immune compromised patients) will be closely monitored and referred to an otolaryngologist if improvement is not evident within days.

The initial treatment of culture negative NOE is empirical. Lohet al [29] has reported no significant difference among treatment outcome between culture specific therapy and culture negative patients who received ceftazidime and oral fluorquinolone. Rubin et al [10] have proposed a combination of rifampicine and ciprofloxacin in the treatment of culture negative NOE. Regardless of the regimen, it appears that dual treatment should be considered in cases of culture negative NOE. Since NOE patients will be subjected to prolonged antibiotic treatment, adverse side effects such as urticaria, neutropenia, hepatotoxicity and others, might be a concern. Schimanteret al [30] reported a higher incidence of adverse drug reactions among NOE patients treated with β -lactamase inhibitors compared with ciprofloxacin. Patients should be monitored periodically during treatment for adverse reaction.

Treatment for mycotic NEO includes amphotericin B, voriconazol, itraconazole and others. Serious adverse reactions to anti-mycotic medications include renal and hepatic failure, hematological abnormalities, arrhythmias and more and patients should be closely monitored. In recent year's liposomal amphotericin B has been indicated for the treatment of invasive fungal infections. Although expensive, it is associated with reduced risk of nephrotoxicity and drug infusion reactions as opposed to normal amphotericin formulation [31] and should be considered for the treatment of mycotic NOE.

Surgery

Prior to the introduction of anti pseudomonal antibiotics, radical surgical intervention was advocated for all patients with NOE. The procedures included extensive removal of all necrotic tissue, including soft tissue, cartilage and bone, mastoidectomy (of different types), and when involved facial nerve decompression. With the introduction of anti pseudomonal antibiotics in the 1980's, the need for early radical intervention has decreased substantially. In the last three decades, surgical intervention has been indicated for: 1) Debridement of necrotic tissue 2) Obtaining deep tissue biopsies 3) Surgical exploration in refractory cases 4) Facial nerve decompression. There is no data in regards to the advantages of surgery in the current treatment modalities of NOE nor is there a clear guideline regarding to the timing or extent of the surgery.

Hyperbaric treatment

Hyperbaric oxygen therapy (HBOT) has been used in cases of NOE. HBOT increases phagocytic killing, increases angiogenesis and has an additive effect to antibiotic treatment [32]. Jefferson et al [33] reported a case series including 16 refractory cases, not responding to adequate antipseudomonal therapy. All patients responded well to 30 days of HBOT treatment combined with antibiotic treatment and no recurrence was reported. Although

promising, a Cochrane review published in 2013 concluded that there is insufficient data to demonstrate the efficacy of HBOT compared to antibiotic and/or surgery for the treatment of NOE [34].

Duration of treatment and follow up

A major question regarding the treatment of NOE is duration of treatment. Several tests and imaging modalities may assist the physician while considering treatment duration. Gallium-67 has been advocated as the imaging modality for the assessment of treatment duration. Since Gallium-67 accumulates in soft tissue as well, technetium-99 is also required for the diagnosis of bone involvement. Okpala et al [21] suggested an investigation protocol in which patients completing treatment should undergo a Tc-99 measurement. Only in the presence of a positive Tc-99 measurement should Gallium-67 scan be performed. Inflammatory markers such as leukocyte count, sedimentation rate and C-reactive protein combined with periodic physical examination may also provide a tool for the assessment of disease progression. Loh et al [29] reported a reduction of 21.7% in the ESR (as compared to initial levels) among patients with resolved NOE, as compared to patients with persistent disease. The same trend was also observed in CRP rates. Currently, there is no data indicating superiority of one method over the other and patient evaluation is performed based on the physician experience and availability of nuclear imaging.

Prognosis

Prognosis of NOE has changed dramatically since Chandler's first description of NOE. Interestingly, despite the lack of consensus regarding the optimal treatment, cure is reported in 87%-100% of cases [11]. Recurrence is reported to occur with a mean rate of 9.6% [11]. There are no known trends regarding timing of recurrence.

Comments

Although known for several decades there are still fundamental issues left unanswered regarding the diagnosis and treatment of NOE. With increasing antibiotic resistance rates, isolating the pathogen and gaining an antibiotic profile are of the utmost importance. Non-PSA NOE and mycotic NOE pose special treatment dilemma, and further data is required for establishing appropriate guidelines. We do, however, believe that cases of NOE not responding to treatment for more than several weeks are highly suspicious for a mycotic NOE and antifungal treatment should be considered.

The role of surgery is still unclear but seems to have a place in refractory and/or culture negative cases. Whether or not surgery should affect treatment duration is unclear. As mentioned above, treatment duration for NOE is similar to the advised treatment duration of osteomyelitis of other bones. Interestingly, a fundamental difference is seen in management, as surgery is commonly performed in osteomyelitis of other bones.

Follow up for patients with NOE may be performed with the help of periodic nuclear imaging or with periodic measurements of inflammatory markers. Regardless of approach used, close evaluation of the affected ear is crucial.

Conflict of interest

The authors have no conflict of interest

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