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OTOLOGY

Management and long-term comorbidities of patients with necrotizing otitis externa

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Abstract

Purpose We aimed to present the management of the patients with necrotizing otitis externa (NOE) and its comorbidities in early and long-term follow-up.

Methods Between 2011 and 2022, 30 patients with the diagnose of NEO, who had cortical bone erosion or trabecular demineralization in temporal bone computed tomography and administered at least 6-week antimicrobial therapy were included in the study. Clinical, laboratory and imaging findings of patients, and comorbidities during follow-up were analysed. NOE extending further from the petro-occipital fissure on magnetic resonance imaging was accepted as medial skull base (MSB) involvement.

Results 30 patients, (8 women, 22 men, mean age 66.2 ± 1.7), with NOE were followed 36.4 ± 29.6 months. The mortality rate was 23.33% and the mean survival time was 12.37 ± 11.35 months. Repeated cultures reveal a new or second pathogen in 5 patients (20%). Severe and profound sensorineural hearing loss (SNHL) were observed in 4 and 12 patients, respectively. Labyrinthitis ossificans emerged in 3 of 6 surviving patients with profound SNHL during follow-up. Chronic disease anemia (CDA) (66.66%), cerebrovascular disease (CVD) (43.33%), chronic renal failure (CRF) (30%), and retinopathy (26.66%) were the most frequent comorbidities in patients with NOE. Cranial nerve paralysis (CNP) ($P < 0.001$), SNHL ($P < 0.04$), CDA ($P < 0.005$), and mortality ($P < 0.022$) were significantly associated with the presence of MSB involvement.

Conclusions NOE is a disease that requires long-term follow-up, causes severe morbidity, and has a high mortality rate. MSB involvement is associated with CNP, SNHL and labyrinthitis ossificans. Moreover, CDA, CVD, CRF and retinopathy are the most common comorbitidies needed to be managed.

Keywords Necrotizing otitis externa · Cranial nerve neuropathy · Tympanomastoidectomy · Facial nerve decompression · Sensorineural hearing loss

Introduction

Necrotizing otitis externa (NOE) is an invasive, potentially life-threatening infection of the external auditory canal (EAC), temporal bone, skull base, and surrounding soft tissue which typically occurs in elderly patients with diabetes mellitus (DM). Pseudomonas aeruginosa (PA) is the most common pathogen; however, other bacteria and fungi are also known to cause NOE [1]. It is presented with the findings of diffuse otitis externa, including granulation tissue that narrows the EAC, persistent otorrhea, and severe otalgia. The facial nerve is the most commonly involved cranial nerve, but abducens, glossopharyngeal, vagus, accessory, or hypoglossal nerves could also be affected. A high index of suspicion, laboratory tests, skull base imaging, culture and sensitivity testing, and histopathologic exclusion of malignancy are required for diagnosis.

NOE was first reported by Toulmouche in 1838 and it was defined as "*malignant*" by Chandler in 1968, but definitive algorithms for the treatment and follow-up of the disease have not been established yet [2, 3]. Before anti-pseudomonas antibiotics surgery was considered the main treatment modality [4]. After introduction of

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anti-pseudomonas antibiotics, the need for radical surgery has been limited. Long-term antimicrobial therapy according to the culture and sensitivity testing is now recommended as the first-line treatment. Patients who do not improve under long-term antibiotic treatment, with persistent symptoms, elevated inflammatory markers, severe otalgia, and cranial nerve palsies could be operated. However, indications, timing, and extent of surgery are still unclear [2]. Deciding when to stop the antimicrobial therapy to prevent the recurrence is also controversial.

We aimed to present management, imaging findings, long-term follow-up, and morbidities of the patients with NOE using data from our institution. We also compared the treatment outcomes and long-term comorbidity between the patients with skull base osteomyelitis limited to the temporal bone and extensive involvement.

Methods

Patients

The study was approved by the Institutional Local Ethics Committee. Between January 2011 and March 2022, patients with NOE who had been hospitalized and administered at least 6-week antimicrobial treatment were included in the study. NOE is diagnosed with clinical, laboratory, and imaging findings. Pathogens were isolated from the affected bones and/or surrounding tissue of all patients. Patients who did not have a follow-up after initial treatment were excluded from the study.

Patient's demographics, concomitant diseases, clinical, laboratory and imaging findings, results of microbiological and histopathological investigations, treatment modalities, times and duration of the hospital stay, and the clinical outcome of at least 12 months of follow-up were recorded. Comorbidities that occurred during follow-up were also noted.

Diagnosis and treatment

All patients had cortical bone erosion or trabecular demineralization on temporal bone computed tomography (CT) at the time of diagnosis. Swab culture and deep tissue biopsy were obtained for microbiologic and histopathologic evaluation. Deep biopsy was performed from more medially located granulation tissues with surrounding edematous skin under local anesthesia. The deep tissue samples are routinely cultured for both bacteria and fungi.

Anti-pseudomonas antibiotic treatment was administered intravenously until the identification of microorganisms. Blood tests including, complete blood count (CBC), comprehensive metabolic panel (CMP), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and procalcitonin examined twice a week. Further antibiotic treatment is administered based on the identification of microorganisms. Repeated deep tissue biopsies were taken for culture in patients with persistent otorrhea and EAC granulation.

Patients underwent daily aural toilette. If the EAC is occluded by granulation tissue, antibacterial, antifungal, and steroid cream-impregnated gauze is embedded tightly four times a day for 1 h. After granulation tissues regress, we apply local treatment at least three times a day including antifungal and antibacterial solutions.

Tympanomastoidectomy with or without facial decompression was performed for the following indications: (1) presence of severe otalgia, excessive otorrhea, EAC granulation disrupting the drainage, and magnetic resonance imaging (MRI) findings compatible with the progression of the skull base osteomyelitis under local and systemic antimicrobial therapy. (2) Worsening of the facial nerve paralysis despite the antimicrobial treatment. (3) Abscess formation in the temporal bone, or epidural and subdural space.

Imaging method and image analysis

CT scans obtained high resolution, 0.5 mm slice-thickness, using a bone algorithm and without contrast administration. Bone erosion and trabecular demineralization were scrutinized in the bony EAC, temporomandibular joint, mastoid tip, petro-occipital fissure, petrous apex, jugular foramen, and clivus. The presence and diameter of a persistent foramen Huschke on the CT at diagnosis were noted. CT images with soft tissue reconstructions were also evaluated for soft tissue swelling with obliteration of fat planes.

MRI of the temporal bone for skull base osteomyelitis was obtained at the time of hospitalization and during follow-up with a 1.5T scan (Magnetom ERA, Siemens Medical Solutions) using an 8-channel head and neck coil. The contrast-enhanced images were obtained after intravenous injection of 10 cc gadoterate meglumine. MRI assessed for the obliteration of the retromandibular fat, and involvement of the soft tissue and bone marrow of the temporomandibular joint. Bone marrow involvement of the ipsilateral and contralateral petrous apex, clivus were evaluated. Skull base involvement extending further from the petro-occipital fissure on MRI were accepted as medial skull base (MSB) involvement (Fig. 1). Abscess formation was defined as a diffusion restriction in nonenhancing fluid collections on diffusion-weighted imaging. Dural involvement was evaluated as a thickening and enhancement of the dura on contrast-enhanced images. Labyrinthitis ossificans was defined as loss of normal high signal of fluid within the inner ear structures on the 3D isotropic high-resolution T2-weighted images. All images were assessed by a senior head and neck radiologist with over 10 years of experience.

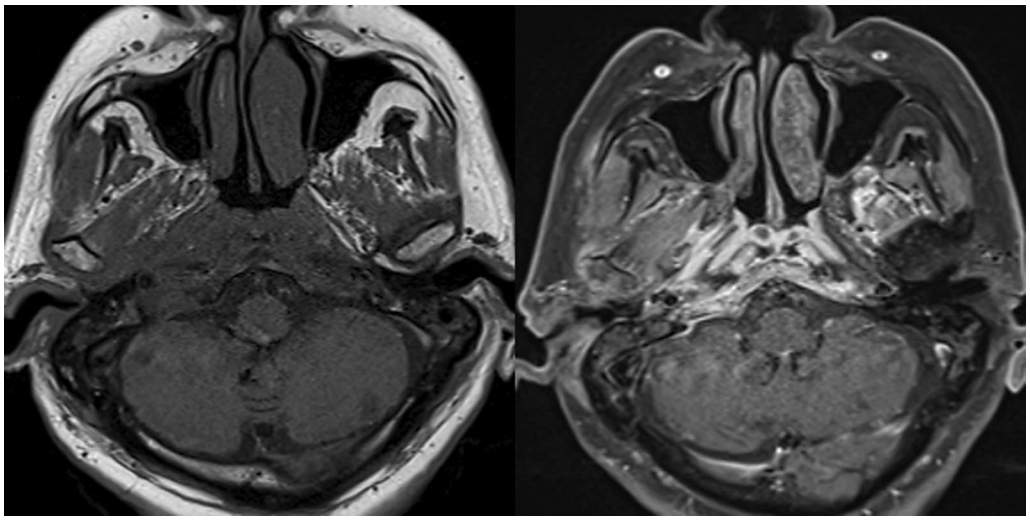

Fig. 1 **a** Axial T1-weighted MRI and **b** axial enhanced fat-saturated T1-weighted MRI demonstrates extensive skull base osteomyelitis in a patient with right-sided necrotizing otitis externa

Follow-up

Patients were discharged with outpatient antimicrobial therapy after remission of clinical, laboratory and imaging findings. Remission criteria were; no need for opioid medication to relieve pain, cessation of abundant ear discharge, and regression of granulation from EAC or mastoid cavity. Outpatient antimicrobial treatment was stopped in patients without otalgia and otorrhea, with epithelialized EAC/mastoid cavity, and marked regression of soft tissue and bone marrow findings on MRI.

Patients were followed-up every 2 weeks after discharge and were followed up every 3 months after antimicrobial therapy were stopped. Inflammation was monitored by CBC, CMP, ESR, CRP, and procalcitonin. Audiometry and balance tests were ordered at least every 12 weeks. Patients had follow-up temporal MRI within a 3-month interval. Regression in soft-tissue findings accepted as a radiologic evidence of improvement. Subsequent involvement of the soft tissue and bone marrow of the skull base medial to the petro-occipital fissure and contralateral side were noted and accepted as an imaging findings of disease progression. Patients are re-hospitalized due to worsening in clinical, laboratory and MRI findings.

Results

Thirty patients (8 women 22 men, mean age 66.2 ± 1.7, range 52–85 years) with NOE were included in the study. The mean age was 60 years for women and 68.5 years for men. 18 patients had NOE on the right side, 10 patients had on the left side, and 2 patients had bilateral NOE. The mean follow-up was 36.4 ± 29.6 months (range 12–120 months). The mortality rate was 23.33% and the mean survival time was 12.37 ± 11.35 months. Predisposing factors, clinical features, and morbidities during follow-up are summarized in Table 1.

30 patients were hospitalized 78 times (range 1–6, mean: $2.6 + 1.42$). The mean duration of the antimicrobial treatment was 24.87 ± 19.4 weeks (range 6–74 weeks). During the follow-up period, a total of 130 cultures were taken from the patients (4.53 ± 2.6 per patient). The pathogen could be determined in 10 of 30 swab cultures, in 18 of 20 deep tissue biopsies, and in 2 skull base bone biopsies. The most common isolated agents were PA (56.66%), methicillin-resistant Staphylococcus aureus (MRSA) (23.33%), Aspergillus species (30%) and other species of bacterial and fungal species (13.33%). Bacteria, fungi and both bacteria and fungi were identified on culture in 16, 2 and 12 patients, respectively, during follow-up in repeated cultures. Aspergillus species and PA coexistence was found most frequently (13.33%). Repeated cultures reveal a new or second pathogen in 5 patients (20%) and antimicrobial treatment changed in 4 of these patients.

Imaging findings are outlined in Table 2. All patients had cortical bone erosion or trabecular demineralization compatible with skull base osteomyelitis on CT. Persistent foramen of Huschke was present in 20 patients (66.6%), and it was larger than 2 mm in 2 patients. The NOE involves the MSB in 20 (66.66%) patients. There was a statistical significance between the presence of MSB involvement and CN palsies ($P < 0.001$), sensorineural hearing loss (SNHL) ($P < 0.04$), chronic disease anemia ($P < 0.005$), and mortality ($P < 0.022$).

Table 1 Predisposing factor, clinical features, and morbidities during follow-up

Predisposing factor, clinical features, and morbidities during follow-up	*n*	%
Predisposing factors		
DM	27	90
External ear canal local trauma or irritation	6	20
Chronic otitis media	12	40
History of the ear surgery	2	6.6
Clinical features		
Severe otalgia resistant to NSAIDs	22	73.3
Granulation tissue in the external auditory canal	28	93.3
Microbiology and pathology		
Swab/debris culture	30	100
Detection of more than one pathogen	10	33.3
Deep tissue biopsy for culture and pathologic evaluation	20	66.6
Skull base bone biopsy	2	6.6
Follow-up and long-term morbidities		
Patients requiring tracheostomy	2	6.6
Multiple hospitalization	20	66.6
Profound sensorineural hearing loss	12	40
Vertigo	10	33.3
Chronic renal failure	9	30
Chronic disease anemia	20	66.6
Cerebrovascular disease	13	43.3
Retinopathy	8	26.6

DM diabetes mellitus, *NSAIDs* non-steroidal anti-inflammatory drugs

Table 2 Incidence of imaging findings

CT and MR imaging findings	*n* (30 patients)	%
CT findings		
Cortical bone erosion[a]	30	100
Persistent foramen of Huschke	20	66.6
MR imaging findings		
Thickening and enhancement of the EAC	22	100
Temporomandibular joint involvement	26	86.6
Skull base involvement medial to the petro-occipital fissure	20	66.6
Contralateral temporal bone involvement	9	30
Dural involvement	12	40
Epidural abscess	4	13.3
Subdural abscess	1	3.3
Labyrinthitis ossificans	3	10

CT computed tomography, *MRI* magnetic resonance imaging, *EAC* external auditory canal

[a]Including the bony EAC, mastoid tip, temporomandibular joint, petrous apex, petro-occipital fissure, foramen lacerum, jugular foramen, and clivus

High procalcitonin level was observed in 9 patients. There was no significance between procalcitonin level and isolation of bacteria, fungi, or both ($P > 0.331$). The ESR was above 20 mm/h observed in 27 patients (Supplemental Digital Content 1 PDF).

Cranial nerve paralysis was observed in 14 patients (Table 3). The facial nerve was the most affected cranial nerve. The degree of facial paralysis was: House–Brackmann grade 6 in 4 patients, grade 5 in 4 patients, grade 4 in 3 patients, and grade 3 in 1 patient.

Tympanomastoidectomy was performed in 12 patients. Facial nerve decompression (FND) was applied with tympanomastoidectomy in 3 patients. FND was performed as a second surgery on 2 patients due to the new onset of facial paralysis after tympanomastoidectomy. Clinical features that affected the tympanomastoidectomy decision were involvement of MSB ($P < 0.07$), facial nerve palsy ($P < 0.02$), severe otalgia ($P < 0.007$), and persistant granulation tissue in EAC ($P < 0.000$). The best improvement in facial nerve functions were observed who received long term antimicrobial therapy regardless of surgery (Table 4).

Severe and profound SNHL was observed in 4 and 12 patients, respectively. Half of the profound hearing loss was bilateral. All these patients had MSB and dural involvement. Six patients (50%) with profound SNHL died within 11 months. We could follow only 6 patients, and labyrinthitis ossificans was determined 3 patients on follow-up MRI (Fig. 2).

MSD involvement was observed in all patients who died. The cause of death of three patients was intracranial hemorrhage due to intracranial spread of the infection.

Discussion

Treatment and follow-up algorithms for NOE have not been determined with a high level of evidence [5]. It can reoccur after treatment and publications related to long-term findings and comorbidities are limited [6]. We presented the management of the patients with NOE, its imaging findings

Table 3 Distribution of cranial nerve involvement

Affected cranial nerve	Ipsilateral paralysis	Bilateral paralysis	Isolated paralysis	Total (*n*)
CN 6	3	0	1	3
CN 7	12	0	7	12
CN 9	1	1	0	2
CN 10	2	2	1	4
CN 11	1	0	0	1
CN 12	1	0	0	1

Table 4 Short- and long-term facial nerve improvement according to the treatment

Treatment method	Facial nerve improvement		
	Total recovery	Partial recovery	Unimproved
Short-term antimicrobial therapy			1
Short-term antimicrobial therapy with TM			2
Long-term antimicrobial therapy	2		
Long-term antimicrobial therapy with TM	2		
Long-term antimicrobial therapy with TM + FD	1	2	2

Short-term treatment: up to 3 months, long-term treatment: more than 3 months

TM tympanomastoidectomy, *FD* facial decompression

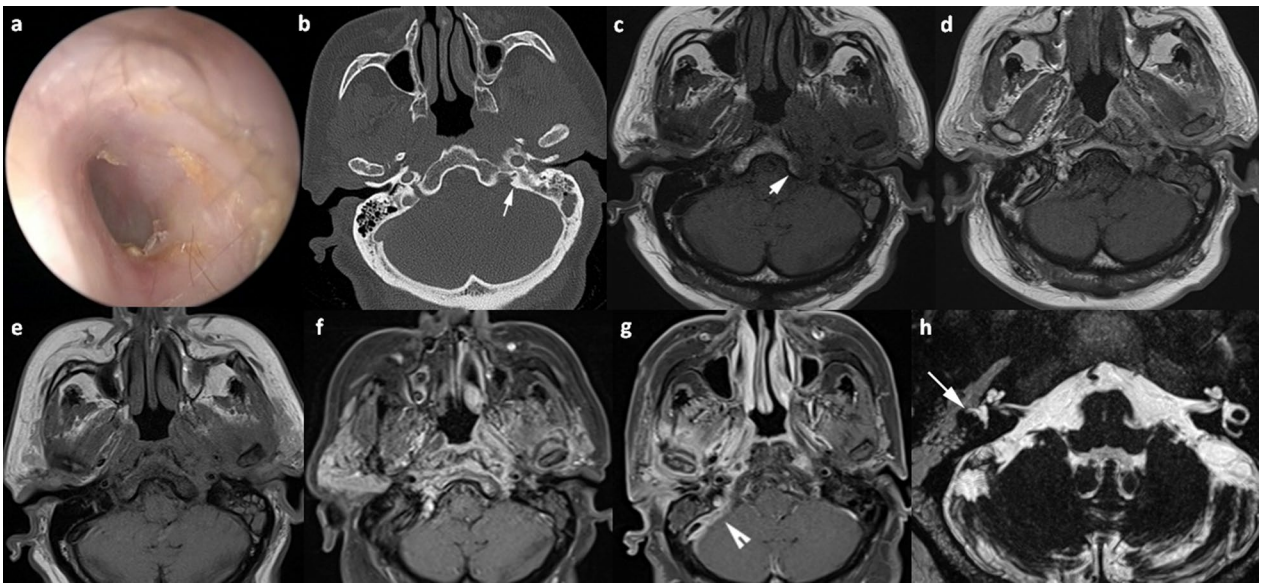

Fig. 2 A 66-year-old woman was treated with the diagnosis of left-sided NOE. At the time of diagnosis, **a** oto-endoscopic view of EAC and tympanic membrane. **b** Axial CT scan through the skull base with bone window demonstrates focal cortical sclerosis and erosions consistent with osteomyelitis. **c** Axial T1-weighted and **d** axial enhanced T1-weighted MR images show obliteration of normal fat planes and involvement of the left temporomandibular joint and nasopharynx. There is also involvement of normal marrow on the left mandibular condyle and left side of the basiocciput (arrow in **c**). After 6 months, the patient's symptoms did not improve and **e** axial T1-weighted and **f** axial enhanced fat-saturated T1-weighted MR images demonstrate involvement of the central skull base. Follow-up imaging was obtained 3 months later. Axial enhanced fat-saturated T1-weighted MR image **g** shows decreased enhancement of the left-side and central skull base bone marrow and adjacent soft tissues but interval worsening of enhancement of the right skull base and dural involvement (arrowhead). During follow-up, the patient developed bilateral profound hearing loss. Axial high-resolution heavily T2-weighted image **h** demonstrates findings of labyrinthitis ossificans in her right ear (arrow). Supplemental Digital Content 2 Video 1, 2, 3, 4 and 5: the oto-endoscopic view of the patient's between November 2019 and June 2021. Anti microbiotherapy was terminated in January 2022. She has no complaints for 8 months and she uses bilateral hearing aids

and comorbidities in early and long-term follow-up in our institution.

Swab sample is generally taken as an initial method before hospitalization. The deep tissue culture and biopsy reveal the causative microorganism at a higher rate. Isolation rates of a pathogen in deep tissue and swab culture were 90% and 33.3%, respectively. We cannot isolate pathogen with the swab and deep tissue cultures in 2 cases. Skull base biopsies are performed from infected bone (clinoid and occipital) and soft tissue determined by imaging under general anesthesia. PCR analysis of tissue samples taken from the EAC can reveal the pathogen [7]. Repeated cultures reveal fungal infection in 4 patients and additional bacterial infection in one patient. Opportunistic fungal infection and unsuccessful sampling due to systemic and local treatment can cause this situation [7].

The ESR, WBC, CRP and procalcitonin have been used for the monitoring NOE. The ESR decreases, while the active disease resolves but it is slower than the WBC count, CRP, and procalcitonin level [8]. The main indication for procalcitonin measurement is to suggest the diagnosis of bacterial infection and to guide antibiotic therapy [9].

However, initial procalcitonin levels were normal in 93.5% of the patients with bacterial NOE in our study. Procalcitonin did not help in distinguishing bacterial or mycotic infections. Only 5 patients with the MSB involvement had a mild increase (< 1 ng/mL), while others had normal (< 0.01 ng/mL) procalcitonin levels during follow-up. However, the CRP and ESR were almost always high in these patients. According to the current study procalcitonin was not useful for monitoring the severity of infection in patients with NOE.

Surgery is required for only selected cases for the treatment of the NOE. There is no clear indications of the timing and extent of the surgery [1]. Canal wall down (CWD) tympanomastoidectomy was done in revision due to the progression of the infection in 2 patients who initially underwent complete mastoidectomy. Thus, CWD tympanomastoidectomy was the final surgical procedure for all patients. We observed higher House–Brackmann grades in patients who underwent tympanomastoidectomy with facial decompression than the patients treated with tympanomastoidectomy and/or long-term antimicrobial therapy. Although this result may be due to the limited number of patients, it indicates that the most effective treatment was long-term antimicrobial therapy. However, we observed that surgery in patients with NOE increased the effectiveness of local and systemic antimicrobial therapy, mostly due to facilitated drainage of the middle ear and mastoid cavity, decreased necrotic tissue load, and removal of micro-abscess and excessive granulation.

In NOE, bacteria, fungi, microbial toxins, and inflammatory infiltrates invade the perilymph and cause toxic labyrinthitis. The labyrinthine infection damages the inner hair cells, enhances the loss of spiral ganglion cells and leads to ossification of the cochlea [10, 11]. We observed 12 patients with profound hearing loss during follow-up and 6 of them were bilateral. All these patients had MSB and dural involvement. Therefore, patients with extensive skull base bone marrow infiltration and dural involvement should be monitored for the SNHL. Labyrinthitis ossificans was observed in 3 of 6 patients with profound SNHL during long-term follow-up.

Temporal bone CT is often first-line imaging for suspected NEO [12]. MRI is superior in evaluating soft-tissue extent, bone marrow involvement, and intracranial complications. Disease extension, progression, and complications during follow-up are best evaluated with MRI [13, 14]. However, MRI findings always lag behind the clinical improvement. Bone marrow abnormalities may persist for weeks to months. Regression of soft-tissue findings is the best imaging finding of early improvement [12]. Although, consensus is lacking regarding the best imaging modality for initial diagnosis and follow-up of NOE, 18F-FDG–PET/CT was found to be superior to Tc99m, Ga67, leukocyte scintigraphy, and MRI for diagnosing NOE [14]. Evaluation of the clinical findings, otorrhea, otalgia, epithelialization in the external auditory canal or cavity, and CRP and ESR along with MRI findings seem to be sufficient in monitoring the NOE. We found MRI also useful for the early detection of the labyrinthitis ossificans in our study.

Cerebrovascular disease (CVD), retinopathy and chronic renal failure (CRF), and chronic anemia were observed higher when compared to the population in the same age group with similar comorbidity. Bacterial and fungal meningitis may cause CVD. Severe inflammation of the skull base leads to activation of coagulation and inhibition of fibrinolysis in the vasculature, which may result in thrombosis, infarction, and hemorrhage [15, 16]. The prevalence of CVD in patients with diabetes is 11.6% among adults age older than 55 years [17]. The CVD was observed in 43.3% of patient in our study.

Our study had several limitations. First, it is a retrospective study with a limited number of patients. However, we followed patients up to 120 months. Second, Covid 19 pandemic caused delays in clinical follow-up in some patients. Thirdly the CT and MRI timing at diagnosis and during the follow-up period was not the same in all patients. Diagnosis of the NEO requires a high index of clinical suspicion, and there is often a delay in diagnosis.

Conclusions

The extent of skull base involvement is associated with CN palsies, SNHL, chronic disease anemia and mortality in patients with the NEO. Procalcitonin may not be a good indicator for infections in the skull base and surrounding soft tissues. The CRP and ESR are more useful for monitoring the NOE. Repeated cultures may be necessary, especially with persistent symptoms or delay in recovery, and it may reveal a second or new pathogen. Patients with facial paralysis have better recovery rates with long-term antibiotic therapy, even if they have decompression surgery. The MSB and dural involvement in patients with the NEO may be a predictor of the development of profound hearing loss. MRI is a promising tool for diagnosis of the NEO, detection of the disease extension and progression, early diagnosis of the intracranial complications and labyrinthitis ossificans. Chronic anemia, CVD, retinopathy, and CRF, were common in patients with NEO and should be kept in mind during the long-term management of patients with NOE.

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Availability of data and materials All data can be available.

Declarations

Conflict of interest There is no conflict of interest for all authors.

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