



Necrotising otitis externa: A single centre experience

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ARTICLE INFO

Article history:
Received 22 April 2020
Received in revised form
10 July 2020
Accepted 22 July 2020

Keywords:
Otitis externa
Fungi
Pseudomonas
Diagnosis
Therapeutics

ABSTRACT

Introduction: Necrotising otitis externa (NOE) is a rare infection of the ear canal with frequent bone erosion. This study's objective is to describe the different features of NOE as well as its management in an ear-nose-throat department. We also tried to identify the particularities of the fungal infection.

Patients and methods: It is an observational cohort that included all the patients hospitalised for the management of NOE. The study was carried out in the ear-nose-throat Department of Mahdia University Hospital in Tunisia between January 2006 and december 2019.

Results: A total of 40 patients were included. The mean age was 65 ± 12.9 years and the sex ratio was 0.9. Ninety percent of the patients included were diabetics. The most common signs found were oedema of the external canal (97.5%) and auricular discharge (92.5%). The main pathogen isolated was *Pseudomonas aeruginosa* (61.7%). Fungi were isolated in 9 cases (26.47%). Computed tomography was performed for 32 patients (80%). Bone erosion was seen in 26 cases (81.3%). The main complications were cerebral venous thrombosis, retropharyngeal abscess and cerebral empyema. Thirty one patients received only antibiotics, 2 received only antifungal treatment, and 7 received both antibiotics and antifungal treatment. All patients had a favorable outcome. Univariate analysis showed a higher median erythrocyte sedimentation rate was associated with fungal infections. No other differences were noted.

Conclusion: Our management protocol seems to be efficient since all patients had initial favorable outcome. A higher median erythrocyte sedimentation rate was associated with fungal infections.

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1. Introduction

Necrotising otitis externa (NOE), also known as malignant external otitis or skull base osteomyelitis, is a severe infection of the ear canal with frequent bone erosion and local complications. NOE is a rare pathology. In United Kingdom, its incidence in general population was estimated to be 10 cases per million per year (District et al., 2015). It classically affects the elderly, diabetic patients or immune-deficient individuals (G Chawdhary et al., 2017). When untreated, NOE is associated with a high mortality, up to 50%. The management of this pathology is mainly medical, based on

antimicrobial agents. When treated promptly, it has a good prognosis (Loh et al., 2019). In Tunisia, we are witnessing a rise in antimicrobial resistance to both antifungal and antibacterial agents (Hadrich and Ayadi, 2018; Résistance bactérienne 2015-2016-2017). So, our management protocols should be reevaluated and updated when needed.

The primary outcome of this study is to describe the clinical, microbiological and radiological features of NOE as well as its management in an ear-nose-throat department. The secondary outcome is to identify the particularities of the fungal infections.

2. Patients and methods

This is a retrospective study carried out in the ear-nose-throat Department of Mahdia University Hospital in Tunisia. It included all the patients hospitalised, for the management of NOE, over a 14 years period between January 2006 and December 2019.

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Peer review under responsibility of PLA General Hospital Department of Otolaryngology Head and Neck Surgery.

Inclusion criteria were:

- Severe persistent otalgia for at least 15 days.
- Physical examination findings in favour with external otitis.
- Unfavourable outcome after initial local or systemic antibiotic treatment.
- Radiological findings showing signs of external otitis when available.

Exclusion criterion:

- Otitis externa with a favorable outcome within a fortnight after local treatment and/or systemic antibiotic treatment with amoxicillin and clavulanic acid.

Data were collected, by the second author, from patients' records with respect of anonymity after the approval of the Ethical Committee of the hospital.

The information collected concerned patients' age, gender, medical history, clinical presentation, microbiological cultures, imaging results, management protocols and outcome.

A superficial swab of the external ear canal was realized for each patient. The microbiological study consisted of a microscopic examination of Gram-stained smears, and cultures onto blood agar and chocolate agar plates for 48 h at 37 °C. Bacterial identification was established using the conventional morphological and biochemical methods. Antibiotic sensitivity was tested with the disk diffusion method and interpreted using the European Committee for Antimicrobial Susceptibility Testing guidelines.

All CT scan images were obtained using a General Electric scanner 16 baretts.

All statistical analyses were carried out using SPSS Statistics Data Editor, version 23. The results were expressed as medians (25–75th percentiles) for continuous variables when Kolmogorov-Smirnov p value was inferior to 0.05 and means \pm standard deviation when Kolmogorov-Smirnov p value was superior to 0.05. Numerical values (percentages) were used for categorical variables. Univariate analysis, a technique of comparing and analyzing the dependency of a single predictor and a response variable, was used to study associations. Comparisons were performed using chi-squared tests for categorical variables (Fisher's Exact Test) and non-parametric Mann-Whitney for continuous variables.

3. Results

3.1. Epidemiological characteristics

A total of 40 patients were included, with a mean age of 65 ± 12.9 years and a sex ratio Male/Female of 19/21. Thirty six patients (90%) had a history of diabetes mellitus; twenty four of them were treated with insulin (66.6%). The 4 remaining patients, aged less than 65 years, had no history of immunodeficiency or underlying pathology (0.1%). The patients' clinical characteristics are presented in Table 1.

3.2. Clinical presentation

The median delay before consultation was 4 weeks [4, 12]. Both the right and the left side were equally affected. The most common symptoms found on physical examination were oedema of the external canal (97.5%) and auricular discharge (92.5%). Table 1 shows the prevalence of symptoms and clinical findings within the studied population.

Table 1
Patients' main characteristics and presentation.

		Number (%)
Characteristics	Male	N = 19, (47.5%)
	Female	N = 21, (52.5%)
	Diabetes mellitus	N = 36, (90%)
	History of antibiotic use	N = 23, (57.5%)
	Right ear infection	N = 20, (50%)
	Left ear infection	N = 19, (47.5%)
	Bilateral infection	N = 1, (2.5%)
Symptoms and clinical findings	Otalgia	N = 40, (100%)
	Oedema of external canal	N = 39, (97.5%)
	Auricular discharge	N = 37, (92.5%)
	Hearing loss	N = 18, (45%)
	Granulation tissue	N = 18, (45%)
	Temporo-mandibular joint pain	N = 9, (22.5%)
	Facial palsy	N = 6, (15%)
	Fever	N = 4, (10%)
	Vertigo	N = 3, (7.5%)

3.3. Microbiology

Microbiologic samples were collected from all infected ears. A pathogen was isolated in 34 cases (85%). The results of the positive microbiological cultures are presented in Table 2. The main microorganism isolated was *Pseudomonas aeruginosa* (61.7%). Twenty antibiograms of *Pseudomonas aeruginosa* were available in the patients' files. Isolated strains were sensitive to ticarcillin (N = 19, 95%), ceftazidime (N = 17, 85%), piperacillin-tazobactam (N = 20, 100%), imipenem (N = 20, 100%), amikacin (N = 19, 100%) and ciprofloxacin (N = 17, 85%). Fungi were isolated in 9 cases (26.5%).

3.4. Imaging

Computed tomography was performed for 32 patients (80%). Bone lysis was seen in 26 cases (81.3%). Temporo-mandibular joint involvement and/or infra-temporal fossa erosion was objectified in 11 cases (34.4%). Extension of the infection to the middle ear was noted in 14 cases (43.8%). Complications found were cerebral venous thrombosis (N = 3, 9.4%), retropharyngeal abscess (N = 1, 3.1%), and cerebral empyema (N = 1, 3.1%). Fig. 1 illustrates some of our patients' computed tomography findings.

3.5. Treatment and outcome

When admitted, 31 patients received only antibiotics (77.5%), 2 received only antifungal treatment (5%) and the 7 remaining patients received both antibiotics and antifungal treatment. When the cultures showed no growth, patients were treated with antibacterial treatment. Initially, all patients received intravenous drugs for a mean period of 28.61 ± 12.9 days. The most used antibiotic association, after results of antibiotic sensitivity tests, was ceftazidime (2g x 3/day) with ciprofloxacin (750 mg x 2/day) in 15 cases (37.5%) followed by imipenem (1g x 3/day) with ciprofloxacin (750 mg x 2/day) in 7 cases (17.5%). Other combinations were used on a case by case basis. The most used antifungal molecule was voriconazole (400 mg x 2/day the first day then 200 mg x 2/day). It was prescribed in 6 cases (15%) to treat infections due to *Aspergillus* and *Candida tropicalis*. The infections caused by *Candida albicans* were treated with fluconazole (800 mg the first day then 400 mg/day). The mean duration of treatment was 40.74 ± 12.93 days. Treatment discontinuation was based on clinical improvement and the decrease of sedimentation rate.

Table 2
Positive microbiologic culture results.

		Number (%)	Number (%)
Bacterial isolates	<i>Pseudomonas aeruginosa</i>	N = 19, (55.9%)	N = 25, (73.5%)
	<i>Staphylococcus aureus</i>	N = 1, (3%)	
	<i>Proteus mirabilis</i>	N = 1, (3%)	
	<i>Escherichia coli</i>	N = 1, (3%)	
	<i>Klebsiella pneumoniae</i>	N = 1, (3%)	
	Mixed pathogens	N = 2, (5.8%)	
Fungal isolates	<i>Aspergillus Flavus</i>	N = 4, (11.7%)	N = 7, (20.6%)
	<i>Candida albicans</i>	N = 2, (5.8%)	
	<i>Candida tropicalis</i>	N = 1, (3%)	
Both fungal and bacterial isolates	<i>Aspergillus Flavus</i> + <i>Pseudomonas aeruginosa</i>	N = 1, (3%)	N=2, (5.9%)
	<i>Candida albicans</i> + <i>Pseudomonas aeruginosa</i>	N = 1, (3%)	

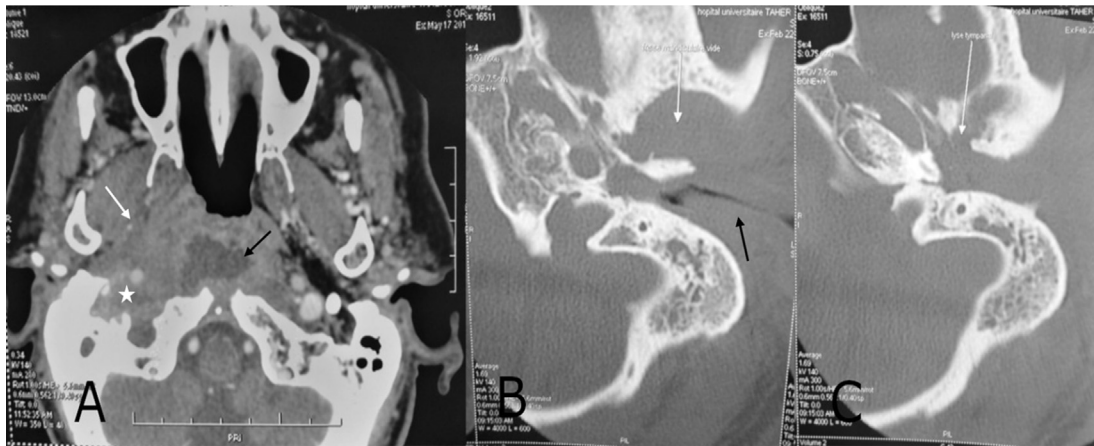


Fig. 1. A. Axial cervical CT image: retropharyngeal abscess (black arrow) with parapharyngeal extension and internal jugular vein thrombosis (white arrow) complicating a necrotising external otitis. B. Axial CT image: thickening and enhancing soft tissue of the external canal (black arrow) with a subluxation and arthritis of the temporomandibular joint (white arrow). C. Axial CT image: Tympanic part of the temporal bone lysis.

The temporomandibular joint involvement didn't require any special management such as a puncture or a surgery. Only one patient kept a trismus. All others recovered without sequelae. Surgical treatment was indicated for one patient who presented with a retropharyngeal abscess. Endobuccal abscess puncture was initially practiced. But the collection persisted, so, a surgical drainage under general anesthesia was performed. After consulting with the neurosurgeons, all the intracranial complications were managed conservatively. Apart from the antibiotic treatment, no other measures were indicated.

After a mean follow up duration of 23.2 months [min = 1, max = 84], all patients had a favorable outcome after initial management judged by clinical improvement and the decrease of sedimentation rate. However, five patients presented a recurrence of the necrotising otitis. These patients received antibiotic treatment guided by antibiogram results with a good outcome.

3.6. Comparison between bacterial and fungal necrotising external otitis

Univariate analysis showed the sedimentation rate was higher in the fungus group compared to the bacteria group. (125 versus 68, p-value < 0.05). No other significant differences were found between fungal and bacterial NOE (Table 3).

4. Discussion

The NOE is a rare pathology that occurs in immunodeficient and

diabetic patients. Our findings were congruent with the literature since 90% of our patients were diabetics. This prevalence is due to microangiopathy, hypoperfusion and compromised immune system (Unadkat et al., 2017). These phenomena explain the invasive character of this infection and the difficulties of management, since hypo perfusion makes it hard to obtain the high antibiotic concentrations compulsory to ensure a favorable outcome. Some authors assimilated NOE to diabetic foot osteomyelitis since they share the same predisposing factors, pathology, and, as a consequence, the same treatment protocols (C. Peled et al., 2018). Four patients had no underlying pathology and were relatively young. Rare cases of NOE were reported within immunocompetent older patients (Unadkat et al., 2017).

There are no consensual criteria that allow the diagnosis of NOE. A group of clinical, radiological and biological arguments are to be associated to retain the diagnosis (Gahide et al., 2013). The diagnosis is usually based on the clinical presentation and the bacteriological findings. The role of imaging could be supportive (Karthik Shamanna, 2018).

Resistance to local treatment, otitis externa, *P. aeruginosa* infection, otalgia, granulation tissue in the ear canal, hyperalgesic form, and local inflammation are the most commonly cited major criteria for NOE (G Chawdhary et al., 2017). Otalgia, otorrhea, and granulation tissue were the most frequent clinical signs, according to different studies (Chawdhary et al., 2015; Gahide et al., 2013; Glikson et al., 2017; Chilaf Peled et al., 2018).

The main pathogen isolated was *P. aeruginosa* followed by fungi. These results are similar to those described in some series (Gahide

Table 3

Comparison between fungal and bacterial necrotising osteitis using Fisher's Exact Test (*) and the non-parametric Mann-Whitney test.

	Fungal infection			Bacterial infection			P value
Diabetes	N = 9, 100%			N = 23, 92%			1*
History of antibiotic use	N = 6, 66.7%			N = 14, 56%			0.7*
Fever	N = 0			N = 3, 12%			0.55*
Hearing loss	N = 4, 44.4%			N = 12, 48%			1*
Facial palsy	N = 2, 22.2%			N = 3, 12%			0.59*
Bone lysis	N = 9, 100%			N = 13, 68.4%			0.47*
Venous thrombosis	N = 0			N = 3, 15.8%			0.53*
Intracranial extension	N = 1, 11.1%			N = 0			0.32*
Recurrence	N = 1, 11.1%			N = 3, 12%			1*
	Median	Q 25	Q 75	Median	Q 25	Q 75	P value
Age	62	56.5	76.5	67	56	78	0.61 ⁺
CRP	23.6	8.25	56.32	7.1	1	55.9	0.2 ⁺
WBC count	8345	7130	11,332	7690	5600	9000	0.36 ⁺
Sedimentation rate	125	68	127	68	38	93	0.049 ⁺

et al., 2013; Glikson et al., 2016; Chilaf Peled et al., 2018). Other studies found that *Staphylococcus aureus* is isolated in second place after *P. aeruginosa* (Hatch et al., 2018).

According to a Survey of Practice Patterns, computed tomography was the method of choice for the diagnosis of NOE followed by technetium scintigraphy. Magnetic resonance imaging was the method preferred to evaluate the extension of the infection (Cooper et al., 2018). A review of the literature concluded that computed tomography is the most available and effective technique to diagnose NOE (Cooper et al., 2018; Glikson et al., 2016; Chilaf Peled et al., 2018). It usually shows bone erosions, central nervous system extension, and soft tissue involvement in the parapharyngeal spaces. Therefore, it is the first test to perform when the diagnosis is suspected (Glikson et al., 2016). In our study, the CT scan wasn't performed in 8 cases for lack of means at the time. Magnetic resonance imaging is more accurate to assess soft tissue and intracranial extension (Gahide et al., 2013). New radiological methods, such as positron emission tomography/computed tomography, are being evaluated regarding treatment discontinuation (Stern Shavit et al., 2019).

In our department, the antibiotic association of choice was ceftazidime with ciprofloxacin. This combination was prescribed empirically in most cases and was continued when the germ isolated in the pus culture was sensitive to these antibiotics. The oral relay, when prescribed, was mainly with ciprofloxacin.

This antibiotic treatment is appropriate to cover *P. aeruginosa*, the main pathogen involved in NOE. This medication regimen also covers most gram-negative bacteria and methicillin-susceptible *Staphylococcus aureus*. These antibiotics also have a wide distribution with a high concentration within soft tissue, bone, and central nervous system. In the United Kingdom, piperacillin/tazobactam is the most commonly used antibiotic. Ciprofloxacin is also recommended as a first-line antimicrobial treatment. Gentamycin is less used and the duration of treatment should be limited to 7 days. Metronidazole and flucloxacillin are prescribed to cover *S. aureus* or anaerobic bacteria (Gaurav Chawdhary et al., 2017). Anti-fungal treatment was only prescribed on culture evidence of fungal growth and after the antifongogram results. It was associated with antibiotics in most cases even when no bacteria were isolated in the swabs. This could be explained by the high rate of prior antibiotic consumption, making it hard to decide if the infection is only due to fungi or if a bacterial infection was associated and the cultures had been sterilized after the antibiotic treatment. This also explains the use of antibacterial treatment when the cultures showed no growth.

In our department, the average duration of systemic antibiotics was 5.8 weeks. Elsewhere, the average total duration of treatment

was controversial ranging between 5.4 weeks (Glikson et al., 2016) and 31 weeks (Loh et al., 2019). Based on recommendations, bacterial NOE should be treated for at least 6 weeks (Courson et al., 2014). For our patients, treatment discontinuation was based on clinical improvement and the decrease of erythrocytes sedimentation rate. No systematic radiological control was performed since all patients had an initial favorable outcome. This attitude is shared by many teams (Loh et al., 2019; Marina et al., 2019). Controlling the imaging could be considered. But, conventional methods that contribute to the diagnosis cannot be used to document resolution. Ga67 scintigraphy or 111In-labeled leukocyte scintigraphy combined with positron emission tomography/computed tomography could help differentiate healing bone from active infection in order to prolong antimicrobial treatment (Courson et al., 2014). The usage of topical therapy, in addition to systemic administration, is controversial (District et al., 2015).

Surgery was only indicated for one patient in our department to drain a retropharyngeal abscess. In cases of NOE, mainly a "local" surgical procedure could be indicated, to remove bone sequester from the external auricular canal, to drain a collection and mostly to obtain histological samples (Gahide et al., 2013).

Hyperbaric oxygen therapy could be beneficial in the management of NOE and it is to be considered for patients who failed conventional treatments and in severe cases. In fact, hyperbaric oxygen therapy amplifies the oxygen diffusion in the infected and avascular tissues which improves leukocytes function and antibiotic concentration in the infected areas. This could help overcome the hypoperfusion and the local immunodeficiency secondary to diabetes. It also speeds the healing since by boosting the osteoid deposition, collagen production, fibroblastic division, and angiogenesis (Amaro et al., 2019; Joana et al., 2019; Mardassi et al., 2016).

The main complication found within our patients was the recurrence of NOE. All over the world, recurrence is common, around 15%–20% (Courson et al., 2014). Mortality remains relatively important and could reach 20% of the cases despite antibiotic therapy. Recurrent NEO is an aggressive disease; conservative surgery should be favoured, if possible, with a better outcome (Omran et al., 2012).

In addition, we tried to define features associated with fungal infection to help evoke this diagnosis. But, except for the higher average erythrocyte sedimentation rate, no other factors were indicative of the fungal origin of the infection. This result could be explained by the longer evolution of the pathology treated initially by antibiotics. Therefore, we witness a rise in the chronic nonspecific inflammation marker (Bray et al., 2016; Glikson et al., 2017).

In addition, these pathogens didn't have any prognostic impact or higher complication incidence. Fungal aetiology is to be

considered in patients suffering from NOE when no improvement is noted despite antibiotic treatment. *Aspergillus* species are the most isolated fungi. Voriconazole is, therefore, the treatment choice in cases of fungal infection (Marchionni et al., 2016).

4.1. Strengths and limitations

Our study is a review of all the patients admitted to our department for NOE. The group of patients had a variable clinical presentation and a relatively high rate of complications that could be explained by the delay before the consultation. The antibiotic sensitivity patterns and the favorable outcome for all patients support the use of the same management protocol. But the high incidence of fungal infections makes it wise to realize a systematic search for fungal agents. The result is to be interpreted on a case by case basis and the specific treatment should be started promptly to avoid complications.

The main limitations of this study were the reduced number of patients (inferior to thirty in each comparison group) and the non-parametric tests used for the statistical analysis. These tests are mainly used when the number of patients is limited and for non-Normal variables. They remain less conclusive than usual parametric tests.

5. Conclusion

Our management protocol seems to be efficient since all patients, presenting with different clinical presentations and various complications, had an initial favorable outcome. A higher median erythrocyte sedimentation rate was associated with fungal infections. No other differences were found between fungal and bacterial NOE.

Declaration of competing interest

The authors have no conflicts of interest relevant to this manuscript to disclose.

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