Necrotising otitis externa: A single centre experience

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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. © 2020 PLA General Hospital Department of Otolaryngology Head and Neck Surgery. Production and hosting by Elsevier (Singapore) Pte Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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 (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; Resistance bacterienne 2015-2016-2017). So, our management protocols should be revaluated 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.
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 bares.

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 ± 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.

| Characteristics                  | 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%) |

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%), pipocilin-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 cefazidime (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 1

| Symptoms and clinical findings | Number (%) |
|--------------------------------|------------|
| 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%) |
The temporo-mandibular 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 \( \text{min} = 1, \text{max} = 84 \), all patients had a favorable outcome 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 hypoperfusion 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). Otolgia, 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 et al., 2013).

| Bacterial isolates | Number (%) | | Number (%) |
|--------------------|------------|---|------------|
| *Pseudomonas aeruginosa* | N = 19, (55.9%) | N = 25, (73.5%) |
| *Staphylococcus aureus* | N = 1, (3%) |
| *Proteus mirabilis* | N = 1, (3%) |
| *Escherichia coli* | N = 1, (3%) |
| *Klebsiella pneumoniae* | N = 1, (3%) |
| Mixed pathogens | N = 2, (5.8%) |
| Fungal isolates | | | |
| *Aspergillus Flavus* | N = 4, (11.7%) | N = 7, (20.6%) |
| *Candia albicans* | N = 2, (5.8%) |
| *Candia tropicalis* | N = 1, (3%) |
| Both fungal and bacterial isolates | | | |
| *Aspergillus Flavus + Pseudomonas aeruginosa* | N = 1, (3%) | N = 2, (5.9%) |
| *Candia albicans + Pseudomonas aeruginosa* | N = 1, (3%) |
was sensitive to these antibiotics. The oral empirically in most cases and was continued when the germ iso-
mism. In the United Kingdom, piperacillin/tazobactam is used and the duration of treatment should be limited to 7 days.

Antibiotics in most cases even when no bacteria were isolated in the pus culture was sensitive to these antibiotics. The oral empirically in most cases and was continued when the germ iso-

cystic fibrosis. 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 NOE 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

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*      |

| Age                      | Median | Q 25 | Q 75 | P value |
|--------------------------|--------|------|------|---------|
| Age                      | 62     | 56.5 | 76.5 |         |
| CRP                      | 23.6   | 8.25 | 56.32|         |
| WBC count                | 8345   | 71.30| 11,332|       |
| Sedimentation rate       | 125    | 68   | 127  |         |

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 fluocoxacin are prescribed to cover *S. aureus* or anaerobic bacteria (Gaurav Chowdhary et al., 2017). Anti-fungal treatment was only prescribed on culture evidence of fungal growth and after the antifungal 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.

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 NOE is an aggressive disease; conservative surgery should be favoured, if possible, with a better outcome (Omran et al., 2012).

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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.

References

Amaro, C.E., Espiney, R., Radu, L., Guerreiro, F., 2019. Malignant (necrotising) externa otitis: the experience of a single hyperbaric centre. Eur. Arch. Oto-Rhino-Laryngol. 276, 1881–1887. https://doi.org/10.1007/s00405-019-04396-7.

Bray, C., Bell, L.N., Liang, H., Haykal, R., Kaiksow, F., Mazza, J.J., Yale, S.H., 2016. Hyperbaric oxygen therapy in the treatment of necrotizing otitis externa: a prospective analysis from the Northern Territory, 1–5. https://doi.org/10.1111/ajr.12469.

Marchionni, E., Parize, P., Lefevre, A., Vironneau, P., Bougnoux, M.E., Poiree, S., Courson, A.M., Vikram, H.R., Barrs, D.M., 2014. What are the criteria for terminating treatment, and outcome in a case series. Diagn. Microbiol. Infect. Dis. 87, 78–84. https://doi.org/10.1016/j.diagmicrobio.2016.10.017.

Hadrich, I., Ayadi, A., 2018. Epidemiology of antifungal susceptibility: review of literature. J. Mycol. Med. https://doi.org/10.1016/j.jmymed.2018.04.011.

Hatch, J.L., Bauschard, M.J., Nguyen, S.A., Lambert, P.R., Meyer, T.A., McRackan, T.R., 2018. Malignant otitis externa outcomes: a study of the university Health-System consortium database. Ann. Otol. Rhinol. Laryngol. 127, 514–520. https://doi.org/10.1177/0001649818787056.

Joana, B.-C., Pereira Diogo, A., Delfim, M., Miguel, V., Tiago, F., 2019. The Role of Hyperbaric Oxygen Therapy in Necrotizing Otitis Externa: A Case Reports Review undefined.

Karthik Shamanna, V.B.G., 2018. Changing trends in the management of malignant otitis externa: our experience. Res. Otolaryngol. 7 (1), 9–14. https://doi.org/10.5923/j.otolaryngology.20180701.03 [WWW Document].

Loh, T.L., Renger, I., Latis, S., Hospital, R.D., Head, O., Surgery, N., Hospital, R.D., 2019. Malignant otitis externa in Australian Aboriginal patients: a 9-year retrospective analysis from the Northern Territory, 1–5. https://doi.org/10.1111/ajr.12469.

Marchionni, E., Parize, P., Lefevre, A., Vironneau, P., Bougnoux, M.E., Poiree, S., Coignard-Biehler, H., DeWolf, S.E., Azemzough, K., Barchiesi, F., Jullien, V., Alario, A., Garcia-Hermosa, D., Waters, M., Kania, R., Lortholary, O., Lanternier, F., 2016. Aspergillus spp. invasive external otitis: favourable outcome with a medical approach. Clin. Microbiol. Infect. 22, 434–437. https://doi.org/10.1016/j.cmi.2015.12.027.

Mardassi, A., Turki, S., Lahlani, R., Mbarek, H., Benzarti, S., Gharsallah, H., 2016. Is there a real benefit of hyperbaric oxygenotherapy in the treatment of necrotizing otitis externa? Tunis. Med. 94, 863.

Marina, S., Goutham, M.K., Rajeshwary, A., Vadisha, B., Devika, T., 2019. A retrospective review of 14 cases of malignant otitis externa. J. Otolaryngol. 44, 63–66. https://doi.org/10.1007/s10542-019-00103-9.

Omran, A.A., El Garem, H.F., Al Alem, R.K., 2012. Recurrent malignant otitis externa: management and outcome. Eur. Arch. Oto-Rhino-Laryngol. 269, 807–811. https://doi.org/10.1007/s00405-011-1736-2.

Pelled, Chlof, El-seid, S., Bahar-dinur, A., Tsvi-ran, L.R., Kraus, M., Kaplan, D., 2018. Necrotizing otitis externa — analysis of 83 Cases: clinical findings and course of disease, 56–62. https://doi.org/10.1097/MAO.0000000000001986.

Pelled, C., Kraus, M., Kaplan, D., 2018. Diagnosis and treatment of necrotising otitis externa and diabetic foot osteomyelitis: similarities and differences. J. Laryngol. Otol. https://doi.org/10.1017/S002221511800013X.

Résistance bactérienne, 2015-2016-2017. Access date: 23-05-2020. URL. https://www.infectiologie.org/resistance.php.

Shram Stav, S., Berstine, H., Sopov, V., Nageris, B., Hilly, O., 2019. FDG-PET/CT for diagnosis and follow-up of necrotizing (malignant) external otitis. Laryngoscope 129, 961–966. https://doi.org/10.1002/lary.27526.

Unadkat, S., Kanbara, T., Watters, G., 2017. Necrotising otitis externa in the immunocompetent patient: case series, 1–4. https://doi.org/10.1017/S0022215117002237.