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OTOLOGY

The significance of tissue biopsy for fungi in necrotizing otitis externa

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Abstract

Introduction The conventional treatment for necrotizing otitis externa (NOE) is prolonged anti-pseudomonas therapy, with surgical treatment in non-responsive patients. The aim of the present study is to describe the course of management of patients with non-responsive NOE undergoing hyperbaric oxygen therapy (HBOT), and to investigate the importance of tissue biopsy for fungi in this group of patients.

Materials and methods A retrospective study conducted between January 2010 and December 2013 at an Otolaryngology Head and Neck Surgery Department. Included were all 52 patients with NOE referred to our Medical Centre for further treatment including HBOT.

Results Fifty-two consecutive patients, 29 men and 23 women, with a mean age of 70.6 years, were included in our study. Twenty seven (51.9%) underwent surgical debridement. No significant difference was found between the group having surgical intervention, and those who did not, with regard to sex, age, comorbidities, cranial nerve involvement or laboratory results. However, those who had surgical intervention had a statistically significant higher rate of fungal infection ($P=0.049$). After completing 7 weeks of HBOT, a significantly lower WBC count was observed in the fungus-infected group (7000 vs 7.800, $P=0.03$), and a tendency towards lower CRP levels in the fungus-infected group (16 vs 58, $P=0.087$).

Conclusion Patients with NOE should have a comprehensive surgical intervention when delayed healing is observed, because proper fungal culturing might change the course of treatment and improve prognosis.

Level of evidence 4.

Keywords Fungi · Necrotizing external otitis · Prognosis · Hyperbaric oxygen therapy · Treatment

Introduction

Necrotizing otitis externa (NOE), also called malignant otitis externa, (MOE) is a devastating disease, most frequently encountered in elderly patients with diabetes mellitus, and in immuno-suppressed patients from all age groups [1–4]. NOE is associated with high morbidity and mortality rates despite adequate targeted antibiotic therapy and prompt surgical intervention. The infection usually originates in the external auditory canal's soft tissue, spreading through the fissures of Santorini to the surrounding tissues to include cartilage and bone of the external ear canal and temporal bone [5]. Spreading to the cranial base is also observed in very advanced cases [6–8]. Patients with NOE resistant to conservative treatment and to surgical intervention are sometimes referred for Hyperbaric Oxygen Therapy (HBOT), with few reports demonstrating this treatment's effectiveness [9]. In these severely diseased ears, the perfusion is poor, resulting in low tissue oxygen tension. HBOT greatly increases the oxygen carried in blood, so that hypoxic tissue can be returned towards or even beyond normal oxygen tension, theoretically enhancing healing [10].

The most commonly reported causative pathogen in NOE has been *Pseudomonas aeruginosa*, followed by *Staphylococcus aureus, Staphylococcus epidermidis, Proteus mirabilis* and *Klebsiella oxytoca* [11–17]. The conventional treatment for NOE is prolonged anti-pseudomonas therapy for at least 6 weeks with intense local conservative treatment. In very advanced cases or in non-responsive

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patients, local debridement and more comprehensive surgical treatment is usually utilized including mastoidectomy and wide local debridement [5]. The debrided tissue should to be sent for further analysis including fungus culture, and often the results are unpredictable. Fungi have been occasionally reported as been involved in NOE, with *Aspergillus fumigatus* the most commonly reported fungal pathogen [17–20].

The aim of the present study is to describe the course of management of patients with non-responsive NOE undergoing HBOT, and to investigate the importance of tissue biopsy for fungal culture in this group of patients.

Materials and methods

The study was approved by the Institutional Review Board. In a retrospective study conducted between January 2010 and December 2013 at an Otolaryngology Head and Neck Surgery Department, 52 consecutive patients, who had failed conventional treatment at other referral tertiary hospitals in the region, were referred to our department for further evaluation and therapeutic management, including HBOT. All patients underwent a physical examination including cranial nerve evaluation, body temperature measurement, daily VAS score evaluation for pain, and routine blood tests that included a complete blood count and c-reactive protein (CRP). The following variables were recorded—age, gender and microbial culture results.

A planar whole body and single photon emission CT (SPECT) Gallium scan was performed in each case as part of the evaluation, and other imaging modalities, computed tomography (CT) scans or magnetic resonance imaging (MRI), were used as necessary.

All patients were treated with broad spectrum antibiotics after consultation with an Infectious Disease specialist, according to culture results.

Only one patient was known to have a fungal infection, while in all others, the infection was suspected of being a resistant bacterial infection. Twenty seven (51.9%) underwent local treatment and surgical debridement of necrotic bone and soft tissue, and tissue for culturing was obtained including for fungi. All patients with proven fungal infection were treated with a 6-week regimen of intravenous Voriconazole. Results of the histopathology of the surgical specimen were retrieved. Our study included only those patients that were treated daily with adjuvant HBOT.

To analyze statistically significant differences in the distribution of categorical variables, χ^2 and Fisher's exact tests were used as appropriate. For statistically significant differences in mean continuous parameters between two groups, Student's *t* test was performed.

Results

Fifty-two patients with NOE were identified during the study period. The study consisted of 29 men and 23 women with a mean age of 70.6 years. Comorbidities included Diabetes Mellitus in 7 patients (13.5%), hypertension in 14 (26.9%) and peripheral vascular disease in 41 (78.8%).

Cranial nerve involvement was found in 24 patients (46.1%), including 14 patients with peripheral facial nerve paralysis. Two patients had glossopharyngeal nerve involvement, five had vagal nerve paresis, one presented with accessory nerve involvement and two had hypoglossal nerve paresis. One of our patients had intracranial involvement.

The mean white blood cell (WBC) count and CRP level at admission were 8.1 (SD 2.3) and 28 (range 18–40), respectively. Ear swab cultures were obtained in all cases, with positive microbiological studies found in 34 (65.4%) patients. *Pseudomonas aeruginosa* was the most frequently occurring organism and was present in 19 (36.5%) cultures. In eight patients, *S. aureus, P. mirabilis* or *Enterococcus* were cultured. Microbiologic studies revealed fungi in 15 patients (28.8%), 9 (17.3%) had Aspergillus and 6 had Candida albicans.

Prior to admission to our department most patients were treated with oral Ciprofloxacin and intravenous Ceftazidime (2 g three times a day). These were ceased on admission to our department. Cultures were taken from the external ear canal and prompt antibiotic therapy was initiated according to microbiologic studies results and pathogen sensitivities. In addition, all patients were treated with Hyperbaric Oxygen Treatment (HBOT), at 2ATA. Forty-four (84.6%) patients completed the planned HBOT (average 30 sessions, range: 23–37). In 2 cases, the HBOT treatment was ceased due to pulmonary edema (both in their 23rd dive), 3 due to worsening disease despite HBOT (after the 7th,17th and 24th dive) and one post head trauma after completing 18 sessions, and another after 23 dives due to sepsis. Only one patient had middle ear ventilation tubes inserted.

Twenty-seven (51.9%) patients underwent surgery as well, including 7 patients who underwent mastoidectomy, 6 patients who underwent debridement of soft tissue and bone of external ear canal and 14 (26.9%) who have had both debridement and mastoidectomy. The decision to operate was made according to clinical, laboratory and imaging parameters; however, the main decision-making parameter was the clinical examination. Patients, who had shown no clinical improvement on physical examination during the course of conservative treatment, or who had severe edema, massive granulation tissue or necrosis of the

Table 1 The patients' parameters according to conservative vs surgical intervention

	Conservative	Surgical	*P* value
Gender, *n* (%)			
Male	14 (56.0%)	15 (55.6%)	0.974
Female	11 (44.0%)	12 (44.4%)	
Age, mean (SD)	70.4 (7.5)	70.8 (11.5)	0.891
DM, *n* (%)	3 (12.0%)	4 (14.8%)	> 0.999
HTN, *n* (%)	7 (28.0%)	7 (25.9%)	0.866
PVD, *n* (%)	19 (76.0%)	22 (81.5%)	0.629
Culture bacteria, *n* (%)	15 (60.0%)	19 (70.4%)	0.432
Culture fungi, *n* (%)	4 (16.0%)	11 (40.7%)	**0.049**
Fever in admission, mean (sd)	36.9 (0.5)	36.7 (0.4)	0.436
WBC in admission, mean (sd)	8.2 (2.0)	7.9 (2.5)	0.776
CRP in admission, median (IQR)	18.0 (10.0–40.5)	30.5 (21.3–40.0)	0.119
VAS in admission, median (IQR)	6.0 (4.8–6.3)	6.0 (5.0–7.0)	0.842
CN involvement *n* (%)	11 (44.0%)	13 (47.5%)	0.427
HBOT treatment number, median (IQR)	30.0 (23.0–40.0)	26.0 (20.0–33.0)	0.204
Pain, *n* (%)	15 (60%)	11 (40.7%)	0.083

Statistically significant value is in bold ($P < 0.05$)

external ear canal tissues on physical examination, underwent surgical intervention. As is shown on Table 1, no significant difference was found between the groups of those who had surgical intervention and those who did not, with regard to sex, age, comorbidities, cranial nerve involvement or laboratory results. However, those who have had surgical intervention have had a statistically significant higher rate of fungal infection ($P = 0.049$).

Further statistical analysis comparing the group of patients with fungal growth to those who were not proven to have fungal infection reveals no difference with regard to sex and age although significantly fewer patients with hypertension were found in the fungi infected group. No difference was found with regard to clinical presentation including body temperature, VAS score, cranial nerve involvement and blood tests (WBC and CRP) (Table2). However, after completing 7 weeks of HBOT, a significantly lower WBC count was observed in the fungus-infected group (7 vs 7.8, $P = 0.03$), and a tendency towards lower CRP levels in the fungus-infected group (16 vs 58 $P = 0.087$).

Five patients died within 60 days after discharge, showing no statistical difference when compared to the survivors in all examined parameters. (60-day mortality is considered as death as a consequence of the disease.)

Discussion

The pathogenic agent of NOE is nearly always bacterial, and very frequently *Pseudomonas aeruginosa*. However, other bacteria and rarely fungi have been reported [21–23]. Therefore, a patient presenting with NOE should be treated empirically with a combination of systemic and local anti-pseudomonal agents for a period of at least 6 weeks, even if the bacteriologic studies will show no growth of any bacteria. The patient's management will also include aggressive control of diabetes, and improvement of immune-competency when possible. However, regardless of the above treatment, various studies report a poor outcome for NOE [24].

Fungal NOE is considered rare and is most often due to *Aspergillus fumigatus*, although cases involving *Aspergillus flavus* and other species have also been reported [25]. The clinical picture of fungal NOE is very similar to that caused by bacteria and according to limited studies might seem to present with worse clinical parameters [26, 27]. However, the diagnosis of fungal NOE is often delayed due to several factors. First, it is usual to initiate anti-pseudomonal treatment even if the bacterial studies show no growth, as this is the most frequent causative pathogen. As the healing effect of antibiotics is expected to be prolonged in this group of patients due to the non-responsive nature of NOE, frequently a significant amount of time elapses before further assessment and to the decision of changing the management protocol. Second, culturing a pathogenic fungus from a swab or pus collected from the tissue bears a very low rate of positive results, and when surgical debridement is not the route of tissue sampling, the chances of revealing fungal infection is low. And finally, there is no one clear clinical, laboratory or radiological parameter that can differ fungal from bacterial infection, apart from tissue sampling for direct smear or PCR [27], and specific fungal culturing; therefore, only surgical intervention can safely exclude the presence of fungal infection. As occurred in our study,

Table 2 The patients' parameters comparing those with proven fungal infection to the group with no fungal involvement

	Culture fungi		*P* value
	No	Yes	
Gender, *n* (%)			
Male	19 (51.4%)	10 (66.7%)	0.314
Female	18 (48.6%)	5 (33.3%)	
Age, mean (sd)	71.5 (9.5)	68.4 (10.2)	0.385
DM, *n* (%)	5 (13.5%)	2 (13.3%)	> 0.999
HTN, *n* (%)	13 (35.1%)	1 (6.7%)	**0.043**
PVD, *n* (%)	28 (75.7%)	13 (86.7%)	0.477
Culture bacteria, *n* (%)	25 (67.6%)	9 (60.0%)	0.603
Surgery, *n* (%)	16 (43.2%)	11 (73.3%)	**0.049**
Fever in admission, mean (sd)	36.8 (0.4)	36.9 (0.5)	0.873
WBC in admission, mean (sd)	8.2 (2.1)	7.6 (2.7)	0.492
WBC in week 7, median (IQR)	7.8 (7.0–10.5)	7.0 (5.0–7.8)	**0.030**
CRP in admission, median (IQR)	24.0 (14.0–37.3)	28.0 (26.0–41.0)	0.166
CRP in week 7, median (IQR)	58.0 (14.5–109.5)	16.0 (13.3–46.5)	0.087
VAS in admission, median (IQR)	6.0 (4.8–7.0)	6.0 (5.0–7.0)	0.592
Involvement CN7, *n* (%)	10 (27.0%)	4 (26.7%)	> 0.999
Involvement CN9, *n* (%)	2 (5.4%)	0 (0.0%)	> 0.999
Involvement CN10, *n* (%)	4 (10.8%)	1 (6.7%)	> 0.999
Involvement CN11, *n* (%)	1 (2.7%)	0 (0.0%)	> 0.999
Involvement CN12, *n* (%)	2 (5.4%)	0 (0.0%)	> 0.999
HBOT treatment number, median (IQR)	30.0 (23.0–37.0)	30.0 (20.0–40.0)	0.855
Complication HBOT, *n* (%)	4 (10.8%)	0 (0.0%)	0.311
Pain, *n* (%)	20 (62.5%)	6 (46.2%)	0.314

Statistically significant values are in bold ($P < 0.05$)

anti-pseudomonas agents were initially started in most of our patients, but the lack of clinical response, or the worsening of symptoms made the diagnosis of Pseudomonas as the pathogen less likely, necessitating surgical intervention and revealing fungal infection.

Our Medical Center is a referral center for patients needing HBOT. Patients with NOE are usually treated elsewhere, conservatively and surgically when needed; however, the more aggressive and non-responsive NOE cases are referred to us for further evaluation and treatment with HBOT. Only one patient was admitted to our department with a proven fungal infection, while the rest were considered as unresponsive bacterial NOEs. A total of 27 patients underwent surgical intervention in our cohort of 52 patients, including 11 who eventually had a proven fungal infection. Significantly more patients with fungal infection underwent surgical intervention, signifying a more clinically aggressive disease. One would expect worse prognosis in that group of patients, with greater morbidity, as have also previously been reported [26, 27]. However, the more comprehensive nature of our management, including surgical treatment in patients with eventually proven fungal infection, might have improved these patients' status and lessened morbidity, as significantly more enhanced healing was observed in the group of patients with fungal infection who had surgical intervention, in contrast to the worse results of treatment in fungal NOE reported in the literature [26, 27].

Comprehensive surgical intervention should be considered in non-healing NOE, allowing proper tissue diagnosis and proper fungal culturing. We assume that the lower morbidity reported in our study compared to the results in other studies can be attributed to the higher rates of fungal culturing initiating antifungal treatment, and to the fact that surgical debridement might have lowered pathogen burden and aided healing.

Conclusion

Patients with NOE with delayed healing should have comprehensive surgical intervention, for debridement and tissue culture for bacteria and fungi, as it might change the course of treatment and improve prognosis.

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Compliance with ethical standards

Conflict of interest There are no possible conflicts of interest.

Ethical approval There are no sources of financial support, corporate involvement, patent holdings, etc., for our research/study; and there is no ethical problem.

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