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OTOLOGY

Malignant (necrotizing) externa otitis: the experience of a single hyperbaric centre

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Abstract

Introduction Malignant otitis externa (MOE) is a potentially life-threatening infection of the soft tissues of the external ear, quickly spreading to involve the periosteum and bone of the skull base. Treatment includes antibiotics and eventually surgery. Hyperbaric oxygen treatment (HBOT) has been proposed as an adjunctive therapy. However, in the tenth consensus conference, this disease was considered as a non-indication for HBOT. The aim of this study was to evaluate the effectiveness of HBOT in MOE treatment.

Methods Retrospective and observational study was conducted of patients with MOE treated in our centre. Staging of the disease was made according to the clinicopathological classification system.

Results From March 1998 to November 2016, 16 patients were referred. 6% patients were on stage 1 of the disease at the time they were referred, 20% in stage 2, 7% in stage 3a, 13% in stage 3b and 53% in stage 4. Seven (43.75%) patients had VII nerve palsy and three (18.75%) patients had multiple nerve palsy. Average length of symptoms of disease was 5 months (maximum 11 months). Average number of sessions was 33 and the length of hospitalization prior to HBOT (median 90 days) was significantly longer than the time between beginning HBOT and cure ($p = 0.028$, Wilcoxon signed rank test). There were no fatalities due to MOE and all patients were considered free of disease after HBOT.

Conclusion HBOT was well tolerated and revealed to be a helpful adjuvant treatment in MOE. According to our data, HBOT should be considered for patients who failed conventional treatments and in severe cases.

Keywords Hyperbaric oxygen · Malignant otitis externa · Necrotizing otitis externa

Introduction

Malignant (necrotizing) otitis externa (MOE) is an aggressive and potential fatal infection. It begins in the soft tissues of the external ear canal and spreads to adjacent structures, such as the base of the skull and temporal bone [1, 2]. This condition occurs mainly in elderly, immunocompromised patients and those with uncontrolled diabetes, although there are case reports in healthy non-diabetic patients [3]. *Pseudomonas aeruginosa* is primarily responsible for most cases of malignant otitis externa [1, 4], but there are cases caused by, *Staphylococcus epidermidis, Proteus mirabilis* and fungal infections [5–7]. Patients with MOE usually complain of ear pain, hearing loss and purulent otorrhoea. On examination you can observe an aural polyp, granulation tissue in the canal and oedema of the external canal. The infection can then spread to the temporomandibular joint anteriorly and to the mastoid and skull base, causing cranial nerves paralysis, venous sinus thrombosis, osteomyelitis and, eventually, death. Usually, imaging examinations such as computed tomography scan (CT scan) and magnetic resonance (MR) are performed to evaluate progression. In some studies, half of the patients with facial paralysis died and of those who survived, half had no return of facial function [1, 5, 8, 9].

Treatment includes antibiotics, with ciprofloxacin being the drug of choice, careful cleaning of the canal with local antibiotics and, eventually, surgery [1]. In severe and persistent cases and where there is no response to oral treatment, the patients have to be admitted to hospital for intravenous treatment usually with a combination of anti-microbial

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regimens [1, 5, 10, 11]. Hospital admission can take several months and it is a potential fatal condition with high mortality in hospital. Hyperbaric oxygenation has been proposed as an adjuvant therapy. It is proposed that hyperbaric oxygenation could bypass the small vessel disease which led to aseptic necrosis, enhancing the infection on the avascular cartilage of the ear canal [12]. However, the lack of prospective and randomized controlled trials supporting the use of hyperbaric oxygen has led to it not being widely accepted [13]. In the tenth European consensus conference on hyperbaric medicine, malignant otitis externa was considered as a non-accepted indication for its use [14]. However, hyperbaric oxygen therapy (HBOT) has been considered in the treatment of various infectious diseases and osteomyelitis [14, 15]. Except for decompression sickness, hyperbaric oxygenation should be regarded as an adjunctive therapy and not as a single therapy choice.

Recurrence has been reported to be around 15–20%, so a 6-monthly follow-up for MOE is recommended [11].

We report the experience of a single hyperbaric centre in the treatment of patients with the MOE in conjunction with antibiotics who have previously responded poorly to conventional treatments.

Methods and materials

A retrospective and observational study was conducted on patients treated at our centre with a diagnosis of MOE. Patients were referred from eight tertiary care hospitals when antibiotics and surgery failed or there was worsening of MOE. We collected data on 21 patients from March 1998 to November 2016. However, because of the lack of clinical information, four were excluded from this study.

The clinicopathological classification system was used for staging MOE [16] at the moment patients started HBOT (Table 1).

The authors contacted the referring eight tertiary care units to confirm if there was relapse of the disease or mortality related to the disease after HBOT.

Mean follow-up was at least 1 year (excluding deaths).

Outcome measures

The outcome measure was disease-specific mortality (died of disease—DOD), died of other causes (DOC), no evidence of disease (cure), and alive but with refractory disease (AWD). AWD was considered if there was incomplete resolution of otalgia, otorrhea, or granulation tissue.

Outcome measures were also length of duration of the disease symptoms previous to admission, duration of inpatient admission (in days), and duration between starting of HBOT and relief/cure of disease (in days).

Facial nerve palsy recovery was also evaluated. However, we did not consider the persistence of nerve palsy as refractory disease, as studies show that not all recover facial function, even when there is no evidence of MOE.

Statistical analysis

Statistical analysis was performed using the IBM SPSS Statistics subscription. For the repeated samples tests, Wilcoxon signed rank test, and for the independent samples, Mann–Whitney *U* test were used.

A value of $p < 0.05$ was considered to indicate a statistically significant difference for all statistical tests.

Hyperbaric oxygen therapy procedure

HBOT was carried out in a multiplace hyperbaric chamber once a day, five times a week. The treatment protocol consisted of 70 min lasting periods of inhalation of 100% oxygen at a pressure of 2.5 ATA, interspersed with one air break lasting 5 min in the middle of the treatment. A cycle of HBOT consisted of 20 sessions or more, depending on the healing results.

Results

Table 2 summarizes the main data of the patients.

Table 1 Clinicopathological classification system for staging MOE

Stage		
1	Clinical evidence of malignant otitis externa with infection of soft tissues beyond the external auditory canal, but negative TC-99 bone scan	
2	Soft tissue infection beyond the external auditory canal with positive Tc-99 bone scan	
3	As above, but with cranial nerve paralysis	
	3a	Single
	3b	Multiple
4	Meningitis, empyema, sinus thrombosis or brain abscess	

Table 2 Data of the patients

Age	Length of disease prior to HBOT (months)	Stage of disease	Length of hospitalization prior to HBOT (days)	Number of HBOT sessions	VII palsy	Other cranial nerv palsy	Internal jugular vein thrombosis	Sigmoid sinus thrombosis	Intracranial complications
83	5	4	90	30	1		1		
82	3	1	30	20					
74	7	2	15	60					
78	4	4	97	20		1			
74	3	2	30	20					
61	6	4	90	40			1		
84	1.5	2	15	20					
70	9	3b	90	30	1				
58	5	4	90	22	1	1	1		1
65	5	4	90	60					1
72	11	4	300	30	1		1	1	
76	5	3a	120	40	1				
56	4	3b	210	80	1	1			
71	3	4	30	20					
69	3	4	30	20	1			1	
70	3	2	80	30					

Patients' characteristics and outcomes

Among the 21 patients analysed, 16 patients completed HBOT. All patients presented with otalgia, otorrhea and granulation tissue. The average age was 71 years and only one patient (6.25%) was female. The average length of symptoms of disease was 5 months (150 days), with a minimum of 3 months and maximum of 11 months. All patients required hospitalization prior to HBOT with a median period of 90 days (interquartile range [30, 94]) with a maximum of 300 days and minimum of 15 days.

The most common imaging modality was a CT scan which was performed in all patients, but seven patients had a magnetic resonance (MRI) and nine patients were monitored with gallium 67.

Classification of the disease in our population was: stage 1 6%, stage 2 25%, stage 3a 6%, stage b 13% and stage 4 50%. Seven (43.75%) patients had VII nerve palsy and three (18.75%) patients had multiple nerve palsy. From those with multiple nerve palsy, one had facial and hypoglossal (XII par) nerve palsy, one patient had facial, oculomotor, trochlear and abducens palsy (III, IV and VI pairs) and one patient had facial, oculomotor, trochlear, abducens, glossopharyngeal, vagus, accessory and hypoglossal nerve palsy (III, IV, VI, VII, IX, X, XI, XII pairs). The patients who had VII palsy displayed a longer duration of disease symptoms (median 150 days) than those who did not have (median 90 days), but it was not statistically significant ($p = 0.142$) (Fig. 1).

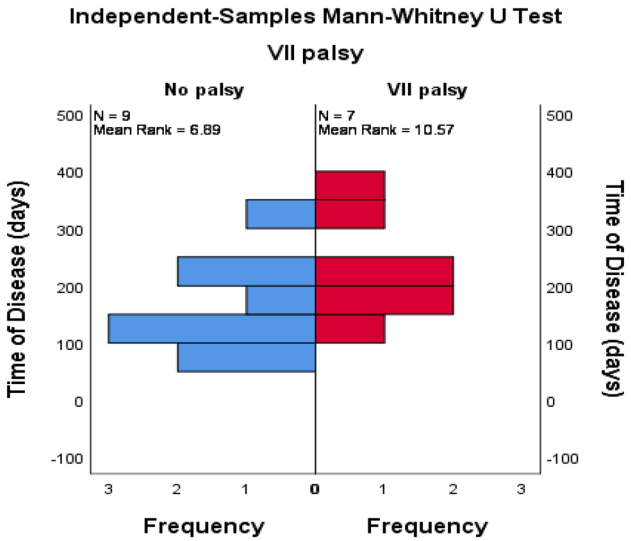

Fig. 1 Comparison of length of disease (days) histograms between patients with VII palsy and those with no VII palsy

All patients had diabetes and one patient also had lymphoma. The most common pathogen identified was *Pseudomonas aeruginosa* (seven patients—43.75%), but *Candida albicans* was also identified in two patients, as well as *Aspergillus flavus, Enterococcus faecalis, Staphylococcus aureus* and *Streptococcus epidermidis*, each in one patient. All patients received antimicrobial therapy in conjuction with HBOT and ciprofloxacin was most often the first-line therapy. Patients were also administered ceftazidime,

ceftriaxone, gentamicin, piperacilin and tazobactam, vancomycin, amikacin, amphotericin, rifampicin, metronidazole and itraconazole, depending on culture results (Table 3).

Nine (56.25%) patients underwent surgery for local debridement or/and decompression of the facial nerve.

The average number of HBOT sessions was 33 with a minimum of 20 and maximum of 80. The median of the duration of HBOT was 42 days (interquatile range [30, 60]). There was no report of adverse effects. The lenght of hospitalization prior to HBOT (median 90 days) was significantly longer than the time between beginning HBOT and cure ($p = 0.028$, Wilcoxon signed rank test).

Of the seven patients with facial palsy, three did not recover (42.8% from the 7 patients with facial palsy) and one had only partial recovery.

The overall disease-specific mortality (DOD) was 0% and referral centres reported that all patients were disease free. One patient died of heart attack after achieving curative treatment (Table 4). Follow-up was for a minimum of 1 year and a maximum of 5 years.

Discussion

MOE is a potentially devastating condition and several series support that severe cases have poorer outcomes [17]. Consensus suggests that the delay in diagnosis resulting in more severe disease is attributed to the variability in the diagnostic criteria [18]. According to some reports, patients have to display at least three of five signs and symptoms of MOE: 1—persistent external otitis; 2—granulation tissue in the external auditory canal; 3—radiographic confirmation of osteomyelitis of the external auditory canal, mastoid air cells or skull base; 4—cranial involvement; 5—isolation of *Pseudomonas aeruginosa* from culture of ear drainage [19]. In fact, Cohen and Friedman suggested that the presence of *Pseudomonas* on cultures is an obligatory diagnostic criterion for this disease [20]. However, diagnosis requires high clinical suspicion since *Pseudomonas* is present as the normal flora of the ear canal, so microbiologic studies might not be sufficient for definitive diagnosis [6, 7, 21]. Therefore, the most common criteria used by most clinicians is the presence of: granulations, otalgia, oedema, otorrhea and resistance to local treatment for at least 8–10 days [10, 16]. The occasional criteria (alone do not establish the diagnosis) are diabetes, cranial nerve involvement, positive radiograph, debilitation condition and old age [20]. Patients included in this study had symptoms present for at least 3 months, with no response to treatment.

CT scanning is the preferred diagnostic modality showing cortical temporal bone erosion and soft tissue involvement, while technetium-99m bone is more sensitive for MOE but lacks specificity. Gallinium-67 scanning shows positive uptake during the active disease process, returning to normal once the infection has resolved. It can be used in monitoring treatment response [22]. The CT scan performed on the patients in this study confirmed infection also present in the soft tissues of the external ear and surrounding structures. It is known for certain that seven patients underwent magnetic resonance imaging (MRI) and nine patients had gallium-67 scanning, confirming MOE and its extension.

As in other studies [1, 17, 23, 24], diabetes or other imunodepressive state were related to the disease in our patients. These conditions, in addition to increasing the incidence of infection, promote diabetic microangiopathy of small vessels, creating ischaemia and hypoxia of soft tissues. Infection itself may also aggravate tissue hypoxia. Facial palsy can be present at the time of diagnosis and it usually is correlated with more severe outcomes and most of the times it does not recover [1, 10, 17]. In our series, we saw full recovery in three patients and partial recovery in one patient. Severe cases experience significantly prolonged treatment courses, surgery and higher relapse rates with more admissions. Actually, in this study, patients with VII palsy showed longer duration of disease than those who did not have VII palsy, though it was not statistically significant.

Pseudomonas is the most common identified pathogen, but it was also the identified fungus in three patients (18.75%). In fact, some authors believe that patients who do not show disease resolution after 7–10 days with antibacterial regimens should switch to empirical antifungal treatments resulting in significant reductions in mortality, morbidity and need for surgical intervention [2]. They consider that there are limitations in culture studies, so early initiation of antifungals can prevent expansion of the infection and cranial nerve involvement. Moreover, as opposed to bacterially mediated disease, fungal infections are known to present with fewer heralding MOE symptoms such as pain and aural fullness and are more closely associated with immunosuppression, leading to diagnostic delays and more severe cases [5, 17]. Other studies report the increasing frequency of non-*Pseudomonas* causes of MOE [25].

In severe cases, because of lack of response with medical treatment, other treatment options are frequently proposed, mainly surgical interventions [1, 17, 19, 22]. In our study, nine patients (56.25%) underwent surgery, but even so the disease was not controlled. Actually, the place of surgery is not well defined in management of MOE. Exposing intact skull bones may on the other side expand infection [26].

Disease resolution is considered when there is pain resolution, no otorrhea or granulation, and when imaging and inflammatory markers are normalized [10].

Because of the high risk of recurrence, follow-up should be at least 6 months [10].

Mortality rate related to MOE can reach up to 42% mainly in severe groups [1, 17, 24]. In a retrospective review of 28

Table 3 Antibiotics used in each patient while on HBOT

Age	Ciprofloxacin	Ceftazidime (g per day)	Ceftriaxone (g per day)	Gentamicin (mg per day)	Piperacilin and tazobactam	Vancomycin	Amikacin	Amphotericin	Rifampicin	Metronidazole	Itraconazole
83	400 mg 12/12 h	3				1 g 12/12 h					
82		3	2	80	4.5 g 8/8 h	1 g 12/12 h					
74	400 mg 12/12 h										
78		3		80							
74		3									
61	400 mg 12 /12 h										
84					4.5 g 8/8 h						
70						1 g 12/12 h		3 g per day	900 mg per day	500 mg 8/8 h	
58		6									200 mg 12/12 h
65	400 mg 12 /12 h										
72	400 mg 12/12 h										
76					4.5 g 8/8 h	1 g 12/12 h	1.2 g per day				
56	400 mg 12/12 h	6									
71											1
69	400 mg 12/12 h										
70		3									

All antibiotics were administered intravenously, except itraconazole that was administered orally. Doses of some antibiotics were adapted according to the renal laboratory tests

Table 4 Outcomes after HBOT

Outcomes	*n*	%
DOD	0	0
DOC	1	6.25
Cure of MOE	16	100
AWD	0	0

patients with MOE treated with antibiotics and surgery, the overall disease-specific mortality was 17.8%, six patients (21.4%) relapsed and two patients were still AWD at the time of the conclusion of the study [17].

In another study with 23 patients treated also with antibiotics and surgery, 9 (39%) patients died because of the disease [1].

In another study with 19 patients, 3 (17%) patients died because of the disease [19].

In Spain, in a retrospective observational study of the population admitted in different hospitals, 355 patients had the diagnosis of MOE and had a mortality rate related to MOE of 3.66% [23].

There was no disease-specific mortality and no relapse in this retrospective study.

Exposure to HBOT can induce vasoconstriction and decreased oedema of damaged tissues, proliferation of fibroblasts, activation of neoangiogenesis, increase in oxygen-dependent antibacterial activity of leukocytes, improved activity of osteoblasts and osteoclasts and increased antibacteiral effectiveness of some antibiotics [8].

The authors of this study believe that it is difficult to perform a double-blind study with HBOT, since the difference of pressures is felt by the human body and because a patient can notice whether he is breathing pure oxygen or air.

Though there are no randomized controlled trials on the use of hyperbaric oxygen therapy in the treatment of MOE [13], this retrospective study demonstrated disease resolution with HBOT in conjunction with antibiotics when all other treatments available failed. The time of hospitalization prior to HBOT was significantly longer than the time between beginning HBOT and cure ($p = 0.028$, Wilcoxon signed rank test). This suggests that the early initiation of treatment with HBOT could prevent severe complications of MOE and the morbidity associated with it.

Conclusion

Malignant otitis externa is a serious disease and our experience demonstrates that HBOT is well tolerated and might be helpful as an adjunctive treatment to microbial therapy. This study supports that HBOT should be considered in patients who failed conventional therapy and in severe cases.

Beacuse of poor accessibility to hyperbaric chambers and relatively rare incidence of MOE, prospective and randomized studies are difficult to conduct, but are needed to support and standardize HBOT treatment protocols.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Research involving human participants and/or animals For this type of study formal consent is not required. This article does not contain any studies with human participants performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study.

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