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MISCELLANEOUS

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Value of hyperbaric oxygen in bacterial and fungal malignant external otitis treatment

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Abstract Malignant external otitis (MEO) is an invasive, morbidity, even mortality, mainly pseudomonal infection of the external auditory canal, frequently involving the base of the skull, multiple cranial nerve and the meninges. In many cases conventional therapy has been prolonged, intensive and relatively ineffective, especially in infections other than bacterial (mainly fungal). We presented theoretical principles of hyperbaric oxygen (HBO) treatment in MEO, our own experience and others' experience in applying this treatment method. We treated eight patients with MEO applying pharmacotherapy, topical management, surgery in one case and also adjunct HBO. In six patients, infection was caused by *Pseudomonas aeruginosa*, in one by *Staphylococcus* sp. and in one by *Aspergillus* sp. Complete recovery was achieved in seven patients. In the patient with MEO caused by *Aspergillus* sp., intracranial complications developed and the patient died. Our experiences in employing HBO in bacterial-caused MEO have confirmed the role of HBO as a valuable, beneficial, supporting classical treatment method. Small number of patients with MEO, especially with non-bacterial infection, and unforeseen clinical course of disease make our experience difficult to objectivize.

Keywords Necrotizing malignant otitis · Osteomyelitis · *Pseudomonas aeruginosa* · Infection · *Aspergillus* sp. infection · Hyperbaric oxygen therapy

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Introduction

Malignant, necrotizing external otitis [necrotizing malignant otitis, pyocyaneus osteomyelitis, malignant external otitis (MEO), progressive necrotizing otitis, pseudomonal granulomatous external otitis, invasive external otitis, necrotizing external otitis, otitis externa diffusa] is a serious, life threatening infection of the skull base, which originates from soft tissues of the external ear canal. This disease mainly affects patients with primary or secondary immunodeficiencies, like older people with diabetes (90% of cases), patients who underwent radio- or chemotherapy, patients with malnutrition or hypogammaglobulinemy [1–5]. Incidents of MEO in children and HIV-positive patients have been reported recently [6].

Etiological agent of MEO is nearly always (98%) *Pseudomonas aeruginosa*; rarely, other bacteria (*Staphylococcus aureus*, *Proteus mirabilis*, *Klebsiella oxyloca*, *Pseudomonas capacia*) or fungi (*Aspergillus*, *Pseudoallos-cheria*, *Candida*, *Malassezia*) [1, 3, 5–13].

Initial symptoms of MEO are not characteristic; they mainly consist of earache and slowly increasing purulent otorrhea. They are usually preceded by microtrauma of the external ear canal skin (cleaning, irrigating). Ineffective local treatment, increasing earache (especially at night), presence of granulomatous tissue at the bottom of the ear canal (at the bone and cartilage border) and deterioration of the patient's general condition should suggest development of MEO [4, 6, 14, 15].

Infection usually spreads along natural fissures, venous canals and fascial junctions, rarely per continuum, towards surrounding anatomical structures, like parotid gland, subtemporal fossa, mandibulotemporal area and skull base, passing through its natural foramens cranial nerves. This might explain the concomitant complications such as parotitis, trismus, paresis of most of the cranial nerves (except I, II and VI), lateral sinus thrombosis, meningitis or brain abscess [4, 6, 14].

Diagnosis of MEO is difficult and may be established after analysis of anamnesis, laboratory tests, radiological (CT scan, MRI, scintigraphy, SPECT), histopathological and bacteriological results. Most authors point out the value of ESR in the assessment of the disease course and treatment results, neglecting the usefulness of leukocytes' count [6, 14]. CT scan allows the proper imaging of density reduction of the skull base, opacification of mastoid, extension of sequesters, destruction of temporomandibular joint and inflammatory lesions of subtemporal fossa soft tissue. However, bony features appear on the CT imaging relatively late, when demineralization reaches at least 30% of the bony tissue, and they persist for a very long time, even when the inflammation is healed. So the value of CT scan in monitoring MEO is limited [16]. MRI is especially valuable in the assessment of soft tissue lesions. In MEO this mainly concerns the inflammatory infiltration of the subtemporal fossa, meninges and marrow cavities of the skull base bones [16]. In bone scintigraphy demineralization is not essential to visualize lesions; more helpful in monitoring MEO is the scanning with Ga^{67} than with Tc^{99} [6]. Promising for more effective diagnosis and treatment monitoring of this disease is the combination of Ga^{67} scintigraphy with SPECT. Histopathological examination determines the nature of the granulomatous tissue taken from the external ear canal (inflammatory or neoplasmatic).

During the past 30 years the treatment methods of MEO have been changing. Therapy should be conducted by otolaryngologists in collaboration with endocrinologist, internist, neurologist, radiologist and microbiologist. Local treatment (with removal of bony sequesters) and systemic antibiotic therapy according to results of bacteriological examinations (aminoglycosides, semisynthetic penicillin, cephalosporines of III and IV generation, fluoroquinolones) is generally accepted [6]. Opinions on usefulness and effectiveness of hyperbaric oxygen (HBO) in MEO are not so concordant [2, 17–20]. The main problem for general acceptance of this treatment method is poor accessibility to hyperbaric chambers and relatively rare incidence of MEO, which makes it difficult to conduct prospective, randomized, double blind trial.

Introduction of fluoroquinolones (especially ciprofloxacin) in MEO treatment was a turn. Their activity against *P. aeruginosa*, good penetration into bones, quick concentration in tissues after oral administration and relatively rare side effects made them a treatment of choice in MEO therapy [15]. Unfortunately the increased resistance of *P. aeruginosa* to ciprofloxacin has been observed lately [21]. For the last few years the tendency to limit surgical procedures has been remarkable—formerly very extended, nowadays only biopsy and sequesters removal. Still, efforts should be taken to compensate glycemia in diabetes patients and improve the immunological condition of all patients. Advances in MEO treatment brought spectacular improvement in treatment results, and mortality decreased from 53.8% [20] to 0–15% [2, 18, 22].

The first description of MEO was presented in 1959 by Meltzer and Kelemen [3], and Chandler in 1968 [1] presented the first comprehensive clinical analysis of 13 cases. In 1983 the first description of a group of 16 patients with MEO treated, among others, with HBO was presented by Lucente et al. [23]. As there have been only few articles on MEO treatment describing greater number of patients, we present our own experience.

Materials and methods

We analyzed eight patients with MEO treated at the Department of Otolaryngology of Medical University of Gdansk and at the National Center for Hyperbaric Medicine in Gdynia in the years 1997–2003. The diagnosis was established on the basis of Levenson et al.'s [15] criteria. Clinical stage was assessed according to Davis et al.'s [2] staging.

At the Department of Otolaryngology, all patients received local treatment of external ear canal using microotoscopy, intravenous and oral antibiotics (fluoroquinolones, III generation of cephalosporines, semisynthetic and polienic penicillins): part of them antifungal and in one patient antromastoidectomy was performed.

Hyperbaric oxygen treatment was conducted at the National Center for Hyperbaric Medicine in Gdynia. It consisted of multiple expositions to HBO, once a day, in multi-seat hyperbaric chamber under a pressure of 2.5 ATA for 70 min, comprising three periods of 20 min for oxygen breathing and two 5 min pauses for air breathing. The pressure was held by compressed air and patients were given 100% oxygen by exact adapted oxygen system with expiration through valves out of the chamber. The total number of expositions for each patient was individually prescribed according to the patient's clinical condition and this was from 14 to 45.

Recovery criteria were as follows: ceasing of headache and otorrhea, improvement in hearing, regression of granulomatous tissue in external ear canal, improvement of neurological symptoms and regression of inflammatory process in the skull base confirmed by scintigraphy. The minimal follow-up period for patients with MEO is 12 months.

Results

Results are given in Table 1. Among treated patients there were five men and three women, age from 44 to 84 (mean 63.7 ± 12.5). In seven patients MEO was diagnosed for the first time; in one patient it was the recurrence of the disease, 21 months after the end of primary treatment (surgery + pharmacology). Seven patients with immunodeficiencies suffered from this disease (diabetes: six patients; severe allergy: one; two diabetic

Table 1 Characteristics of MEO patients treated by hyperbaric oxygenation (HBO)

No.	Initials	Sex/age	Concomitant diseases	Symptoms	Diagnostic imaging	Bacteriology	Clinical phase	Treatment			Treatment result/follow-up period (months)
								S	Ph	HBO/(exp.)	
1	T.H.	F/44	A	H, O, Ha	RTG, CT, SCT	*Pseudomonas aeruginosa*, *Candida parapsilosis*	I	–	FQ, SP, AM	20	Recovery/42
2	B.S.	M/64	DM, Ne	H, O, Ha	RTG, CT	*Pseudomonas aeruginosa*	I	–	FQ, SP	14	Recovery/45
3	O.T	F/52	DM, Ne	H, O, Ha, Pn: VII	RTG, CT	*Pseudomonas aeruginosa*	I	–	FQ, SP	25	Recovery/46
4	W.L.	M/74	DM	H, O, Ha, Pn: VII, IX, X, XI, XII	CT, MRI, SCT	*Pseudomonas aeruginosa*	II	–	FQ, CE	20	Recovery/14
5	W.M.	M/71	DM	H, O, Ha, Pn: VII, IX, X, XI, XII,	RTG, CT, SCT	*Staphylococcus aureus*, *Staphylococcus epidermidis*, *Candida albicans*	II	–	FC, SP, AM	16	Recovery/48
6	P.J.	M/84	DM	H, O, Ha, Pn: VII, X, XI, XII	RTG, CT, MRI, SCT	*Pseudomonas aeruginosa*, *Staphylococcus aureus*	II	+	FQ, SP, CE	45	Recovery/12
7	S.U.	F/57	–	H, O, Ha, Pn: VII	RTG, CT, MRI, SCT	*Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Prevotella* sp.	II	–	FQ	32	Recovery/4
8	B.J.	M/65	DM	H, O, Ha, Pn: III, V, VI, VII, IX, X, XII	RTG, CT, MRI, SCT	*Aspergillus* sp.	III	–	FQ, CE, AM	16	Death

M Male, *F* female, *A* allergy, *DM* diabetes, *Ne* neoplastic disease, *H* headache, *O* otorrhea, *Ha* hypoacusis, *Pn* nerve paresis, *SCT* bone scintigraphy, *S* surgical treatment, *Ph* pharmacotherapy, *FQ* fluoroquinolones, *SP* semi-synthetic penicillin, *CE* cephalosporines, *AM* antimycotic

patients were, in the meantime, treated for malignant neoplasms); in one patient no dependence was found. The following etiological agents were found: *P. aeruginosa*, six patients; *Staphylococcus* sp., one patient; *Aspergillus* sp., one patient. In three patients, clinical stage I was diagnosed, in four stage II and in one stage III. Radiological imaging proved osteomyelitis at the skull base in four patients—in these patients scintigraphy Tc^{99} was performed. Complete recovery was achieved in seven patients. In one patient with MEO caused by *Aspergillus* sp., intracranial complications developed and the patient died.

Discussion

Most of the authors connect increased incidence of bacterial infections in diabetic patients (a.o. *P. aeruginosa* and development of MEO) with ischemia and hypoxia of soft tissues of the ear and temporal bone and this is thought to be a result of diabetic microangiopathy of small blood vessels. Infection itself may also be a reason for tissue hypoxia. Impaired oxygen supply disables oxygen-dependent antibacterial activity of leukocytes by inhibition of free radicals production [24]. Together with increasing hypoxia, bactericidal activity of aminoglycosides decreases [25].

Necrotizing inflammation of soft tissues and resistance to osteomyelitis treatment are generally accepted indications, by national hyperbaric medicine societies, American Undersea and Hyperbaric Medical Society (UHMS) and European Committee for Hyperbaric Medicine (ECHM), for HBO therapy [24]. Rationality of HBO treatment in this disease has been proved in experimental and clinical trials. The following changes resulting from exposition to HBO were observed: vasoconstriction and decreased edema of damaged tissues, proliferation of fibroblasts, activation of neoangiogenesis, increase in oxygen-dependent antibacterial activity of leukocytes, improved activity of osteoblasts and osteoclasts, increased antibacterial effectiveness of some antibiotics [7, 24, 26].

Rarity of MEO incidence, difficulty in foreseeing it, often poor outcome and low accessibility to hyperbaric chambers are serious problems in conducting prospective, randomized, double blind clinical trials on the value of HBO treatment in MEO. Papers published till now on indications, contraindications and results of HBO in this disease are based on authors' own experiences and conclusions from others' result observations.

A clinician employing HBO in MEO treatment highly estimates its therapeutic value. Shupak et al. [19] suggested that HBO should be applied to each case of MEO. Tisch et al. [22] recognized the effectiveness of HBO and introduced this method in German military hospital as a standard of MEO treatment. Davis et al. [2] found particular benefits of HBO in advanced clinical stages of MEO (stages II and III), recurrence of the disease and in patients resistant to antibiotics therapy.

In textbooks and articles, there are several opinions concerning HBO value in MEO treatment, regarding the other authors' opinions and experiences. Tos [27] found the addition of HBO to actual treatment methods beneficial. Handzel and Halperin [14], although supporting the antibiotic therapy effect of HBO, found its complicated procedure as the main disadvantage of HBO. Vernick [20] denies MEO treatment with HBO is beneficial, pointing out high costs, time costing and lack of reliable clinical trials. In some other papers on MEO treatment, HBO was not even mentioned as a treatment option [3, 5, 9, 12, 15, 21].

Treatment results of our patients are satisfactory; in our study, only in one patient (case nr 8) was our treatment unsuccessful. Despite negative bacteriological investigations for the presence of *P. aeruginosa*, severe headache, palsy of VII, IX, X and XII nerves diabetes and extended inflammatory infiltration of the skull base in MRI made us introduce antibacterial and HBO treatment. After no improvement in the 14-day therapy, serologic test for antimycotic antibodies and subsequent bacteriological investigations allowed to diagnose otogenic skull base osteomyelitis caused by invasive *Aspergillus* sp. infection. Despite antimycotic treatment (amphotericin, itraconazole) and continuation of HBO, the patient died (53 days after admission to the ENT Department). Autopsy revealed extensive mycotic infiltration of the skull base with involvement of the dura of left middle cranial fossa and fungal emboli in distal branches of pulmonary artery. Light microscope investigation confirmed the presence of *Aspergillus* sp. Delayed diagnosis of otogenic skull base osteomyelitis caused by invasive fungal infection was also described by others in some papers concerning this problem [7–9]. Since 1985, when Petrak et al. [11] presented a case of *Aspergillus* sp. caused MEO, there have been 24 case reports of this kind of infection found in literature [10, 11]. Only in one of them [7], HBO was applied as a treatment method, despite the well-known inhibiting influence of HBO on the growth of fungi [28–30]. Our report of MEO caused by *Aspergillus* sp. is the twenty-fifth published in the literature and the second in which HBO was used as a treatment method [5, 10, 12, 13]. Menchof and Jackler [8] investigating differences between *Pseudomonas* sp. and *Aspergillus* sp. caused MEO found that fungal infections are more frequent in older patients or patients with immunodeficiencies than in those with diabetes. The fungal infection usually originates from chronic otitis media, and biopsy is essential for establishing the diagnosis (especially when antibacterial treatment fails) [8].

Conclusion

Our experiences from the last few years in employing HBO for bacterial MEO have confirmed the role of HBO as a valuable, beneficial, supporting classical treatment method. Treatment of a patient with *Aspergillus* sp. caused MEO failed, and upon this single case we are not authorized to assess the value of HBO in fungal MEO treatment. Small number of patients with MEO, especially non-bacterial, and unforeseen clinical course of the disease make our experience difficult to objectivize.

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