MALIGNANT EXTERNAL OTITIS. A CASE SERIES FROM AN ITALIAN TERTIARY-CARE HOSPITAL

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ABSTRACT

***Objectives**: Malignant external otitis (MEO) is an aggressive and potentially fatal disease that affects the external auditory canal (EAC); it occurs almost exclusively in elderly, diabetic patients or immune-compromised ones. The aim of this study was to describe epidemiological and clinical characteristics of a consecutive series of patients affected by malignant external otitis (MEO) and to conceive a flow-chart for its management.*

***Material and methods**: Adult patients diagnosed with and treated for MEO at the University Hospital of Messina, Italy between 2003 and 2013 were identified. Charts were reviewed for history, clinical presentation, laboratory data, treatment, and outcomes.*

***Results**: Data of 11 patients were analyzed. Patients' mean age was 67.6 years, and ten were males. All but one suffered from diabetes and one was HIV infected. Average time of arrival at our department from onset of symptoms was 12.3 weeks. Intravenous antibiotics were administered in seven cases whereas exclusively oral antibiotics were given to four patients. Local antibiotic therapy was associated to systemic administration in seven cases. Four patients underwent surgical treatment. The median duration of antibiotic treatment was 12.4 weeks. Ten patients experienced a complete recovery even if in one of these residual facial palsy was reported; one patient died of a skull base osteomyelitis with multiple nerve involvement. A flow-chart which could guide physicians in the management of MEO is proposed.*

***Conclusions**: Malignant external otitis still remains today a very challenging issue. Randomized clinical trials are needed to better clarify which medical and surgical treatment could be the gold standard. A consensus diagnostic flow diagram could help in the management of this pathology.*

***Key words**: Fluoroquinolones, Malignant external otitis, Pseudomonas aeruginosa, Tc-sulesomab.*

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Introduction

Malignant external otitis (MEO) is an aggressive and potentially fatal disease that affects the external auditory canal (EAC); it can spread through the fissures of Santorini and the osseous-cartilaginous junction[1]. This rare disorder occurs almost exclusively in elderly, diabetic patients or immune-compromised ones[1]. Today there is no data about incidence of MEO. *Pseudomonas aeruginosa* is the most common infectious agent but other microorganisms such as *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Proteus mirabilis*, *Klebsiella oxytoca*, *Klebsiella pneumoniae*, *Candida albicans* and *Aspergillus fumigatus* have been associated with MEO[2,3]. The infection may be polymicrobial[4].

It is thought that microangiopathy in the ear canal predisposes elderly diabetic patients to MEO[5]. Occurrence in children is rare and associated with diabetes, anaemia, malnutrition, and chemotherapy treatment[6]. Dermatitis of the EAC, concurrent medication with antibiotics, recent ear irrigation are other promoting factors[1].

In this paper, epidemiological and clinical data of patients affected by MEO and admitted consecutively to our hospital over an 11-year period were retrospectively evaluated.

Materials and methods

The AOU Policlinico "G. Martino" of Messina, Italy, is a tertiary-care university hospital with 650 beds serving a population of about 1,000,000 in eastern Sicily and southern Calabria. All patients diagnosed with MEO consecutively from January 2003 through December 2013 were included in this study. Patient's clinical histories were stored in a database that included demographic characteristics (age, sex), clinical and laboratory findings recorded on admission and during hospitalization, therapeutic interventions, and clinical outcome.

Diagnosis of MEO was established, as suggested by Cohen[7], in the presence of "obligatory" criteria (pain, oedema, exudate, granulations, micro-abscess (when operated), or failure of local treatment (>1week). The presence of "occasional" criteria (diabetes, cranial nerve involvement, positive scan, debilitating condition and old age) alone was not considered sufficient for diagnosis of MEO[7].

ment and was defined as cure or failure in the case of persistence or worsening of clinical and laboratory findings. Relapse was defined as the reappearance of signs and symptoms of disease after initial successful treatment.

Results

In the study period, 11 patients were diagnosed with MEO. Admissions averaged one per year, without any seasonal variation. All patients had previously been treated in other hospitals or clinics when they came to our observation. Data regarding clinical characteristics, therapy and outcome of these patients are analytically shown in table 1.

Patients' mean age was 67.6 years (range, 48-83 years), and ten were males. Regarding comorbidities, 10/11 suffered from diabetes (type 1 in one case, and type 2 nine cases) with a mean HbA1c of 7.6%. Three diabetic patients were poorly controlled (HbA1c >8%). One patient was HIV infected.

Patient#, age/sex	Comorbidities	HbA%	Predisposing factors	Previous antibiotic treatment and (duration)	Symptoms	Physical examination	Microbiology	ESR (mm/h)	CRP (mg/l)	WBC (× 10³/l)	CT findings and anatomic structures involvement	MRI and Leukoscan findings	Histo-Pathology	Antibiotic (duration)	Surgery	Outcome clinical exam findings and Imaging findings	EOT ESR (mm/h)	EOT CRP (mg/l)	EOT WBC (× 10³/l)
1, 71/M	DM2	7.2	no	amoxicillin-clavulanic acid PO + local tobramycin (18 W)	otalgia/otorrhea intraparotid adenopathy/temporomandibular symptoms/facial palsy	EAC stenosis/Granulation tissue	*P. aeruginosa* + *S. epidermidis*	163	12.4	15250	Soft tissue in EAC/erosion EAC/TMJ /mastoid /middle ear/parotid	MRI Leukoscan:abnormal tracer uptake	ND	PO ciprofloxacin 750 mg bid (14 W)	no	Cured CT: Erosion EAC/TMJ Leukoscan	13	1.2	7330
2, 66/M	DM2	6	termal spa	local + levofloxacin PO (13 W)	otalgia/otorrhea/mastoid swelling/temporomandibular symptoms	EAC stenosis/Granulation tissue	*P. aeruginosa* + *P. mirabilis*	177	13.6	15670	Soft tissue in EAC/erosion EAC/TMJ /mastoid	NO	YES	PO ciprofloxacin 750 mg bid (11 W) + local	yes (debridement)	Cured CT: Erosion EAC/TMJ	11	1.2	5340
3, 74/M	DM 2	8.6	no	yes, unknown (12 W)	otalgia/otorrhea/temporomandibular symptoms	EAC stenosis/Granulation tissue/EAC polyp	*P. aeruginosa*	20	0.3	7700	Soft tissue in EAC/ erosion EAC/TMJ I	NO	YES	IV levofloxacin 500 mg bid then IV ciprofloxacin 400 mg bid (total 11 W) + local	no	Cured	18	0.1	7320
4, 83/M	DM 2	7.5	no	ceftaxidime IM, ciprofloxacin PO and local tobramycin (14W)	otalgia/otorrhea/facial palsy	Granulation tissue	*P. aeruginosa*	22	6.1	8600	Soft tissue in EAC/ erosion EAC/mastoid /middle ear	MRI Leukoscan: abnormal tracer uptake	ND	IV vancomycin 500 mg qid followed by teicoplanin 400 mg bid + ceftrixone iv 2 gr qd (20 W) + local	no	Cured CT: Erosion EAC/TMJ Leukoscan	9	0.4	4800
5, 68/M	DM 2	6.3	no	Ceftrixone IM then ciprofloxacin PO (17 W)	otalgia/otorrhea/mastoid swelling/facial palsy	EAC stenosis/Granulation tissue	*P. aeruginosa*	110	8.5	8700	Soft tissue in EAC/ erosion EAC/mastoid/middle ear	MRI Leukoscan: abnormal tracer uptake	ND	PO ciprofloxacin 750mg bid+ IV gentamicin (2 W) (total 13 W) + local	Facial nerve decompression	Persistent facial palsy, soft tissue in EAC CT : Soft tissue/erosion EAC/mastoid/middle ear	21	1.4	7880
6, 72/M	DM2	8	NO	Levofloxacin PO (12 W)	otalgia/otorrhea/mastoid swelling	EAC stenosis/Granulation tissue/EAC polyp	*P. aeruginosa* + *S. epidermidis*	86	3.8	9800	Soft tissue in EAC/ erosion EAC/middle ear /skull base	MRI	YES	IV vancomycin 500 mg qid then PO linezolid 600 mg bid then PO ciprofloxacin 750mg bid (total 12 W)	yes (debridement)	Cured CT : erosion EAC/skull base	8	1.05	7550
7, 70/M	DM 2	7.4	NO	amoxicillin-clavulanic acid PO (8 W)	otalgia/otorrhea	Granulation tissue/EAC polyp	*P. aeruginosa*	20	0.5	6800	Soft tissue in EAC	NO	YES	IV ciprofloxacin 400 mg bid (9 W) + local	yes (biopsy)	Cured	11	0.4	6500
8, 48/M	HIV	ND	NO	Ceftazidime IM (4W)	otalgia/otorrhea	EAC stenosis/Granulation tissue	*S. marcescens* + *S. fonticola*	23	0.08	3800	Soft tissue in EAC/ erosion EAC	NO	YES	IV levofloxacin 500 mg bid (8 W)	yes (biopsy)	Cured	15	0.08	3500
9, 51/F	DM 1	7.5	irrigation	levofloxacin PO (16 w)	otalgia/cephalalgy/fever/ cranial nerves involvement XI-XII)	EAC stenosis/ Granulation tissue	*S. epidermidis* *P. aeruginosa*	112	2.8	12000	Soft tissue in EAC/ erosion EAC/middle ear /skull base	MRI	YES	IV ciprofloxacin 400 mg bid (18 W)	Yes (debridement)	Died for osteomyelitis of skull base			
10, 72/M	DM 2	8.9	ear swab	amoxicillin-clavulanic acid PO (13 w)	otalgia	EAC stenosis/Granulation tissue	*S. marcescens* + *S. fonticola*	34	0.8	15400	Soft tissue in EAC/ erosion EAC	NO	ND	PO ciprofloxacin 750 mg bid (12 W) + local	no	Cured	12	0.6	8560
11, 69/M	DM 2	9.3	ear swab	ciprofloxacin PO (9 w)	otalgia	Granulation tissue	*P. aeruginosa*	21	0.3	12450	Soft tissue in EAC	NO	ND	PO ciprofloxacin 750 mg bid (9 W) + local	no	Cured	15	0.2	8960

Table 1: Clinical characteristics, therapy and outcome of 11 patients with Malignant external otitis.
Bid, twice a day; EOT, end of treatment; ND, not done; PO, by mouth; qd, every day; qid, four times a day; tid, three times a day; W, weeks

Dossiers with doubtful diagnosis and incomplete clinical data were excluded from the study. Clinical response was assessed at the end of treat-

Two had undergone traumatic maneuvers before the onset of infection (cleaning of EAC with ear swab), while one patient underwent extraction

of cerumen plug and one patient had performed thermal therapy previously.

Clinical presentation at the time of admission

All patients presented with unilateral otalgia, 8/11 with otorrhea, 4/11 with initial cranial nerve lesion (three, facial nerve palsy, one XI-XII nerves palsy), 3/11 complained of temporo-mandibular joint (TMJ) symptom, 3/11 with mastoid region swelling, and one complained of cephalalgia, one with fever and one with intraparotid lymphadenitis. Otoscopic examination highlighted granulation tissue in all cases, stenosis of external auditory canal in 8/11 patients, and polyp in 3/11 cases.

All patients had received systemic antibiotic therapy before admission: fluoroquinolones in 6/11 cases; cephalosporins in 3/11 cases; amoxicillin/clavulanic acid in one case. In 2/11 cases tobramycin drops had been administered locally. Average time of referral to our department after the beginning of first cycle of therapy was 12.3 weeks (range, 4-18 weeks).

Microbiology

In five cases the infection was monomicrobial and caused by *P. aeruginosa*, and the remaining six were polymicrobical: *Serratia fonticola* and *Serratia marcescens* in two cases, *P. aeruginosa* and *S. epidermidis* in two cases, *P. aeruginosa* and *Proteus mirabilis* in two cases.

Laboratory parameters, Imaging and Histopathologic examination

At admission, erythrocyte sedimentation rate (ESR) mean value was 71.6 mm/h (range 20-177); mean C-reactive protein (CRP) 4.4 mg/l (range, 0.3-13.6 mg/l); mean white blood cells (WBC) count 10561 × 10^9/l (range, 3800-15670).

All patients underwent computed tomography (CT) scan, five patients underwent magnetic resonance imaging (MRI), and 99mTc-sulesomab (LeukoScan; Immunomedics Europe, Hillegom, The Netherlands) scan was performed in three cases. In all cases, CT scan showed presence of soft tissue in the EAC. In 9/11 cases an erosion of the walls of the EAC was highlighted. Other imaging findings included: mastoid involvement in 5/11 cases, middle ear involvement in 5/11 patients, TMJ involvement in 3/11 cases, skull base involvement in 2/11 patients. MRI was performed on the basis of CT scan findings (mastoid, middle ear, parotid and skull base involvement). 99mTc-sulesomab scan revealed an abnormal tracer uptake in the same areas highlighted by CT scans suggesting a focal inflammatory/infectious process consistent with MEO in the three cases in which it was performed.

Treatment

The first objective of our therapy was the control of diabetes. Intravenous (IV) antibiotic therapy was administered in 7/11 cases, associated to oral (PO) antibiotics in two patients; PO therapy only was administered in four patients. In 7/11 patients a local antibiotic therapy was also associated. Monotherapy with fluoroquinolone was administered in 8 cases (PO ciprofloxacin 750 mg bid in four cases; IV levofloxacin 500 mg bid then IV ciprofloxacin 400 mg bid in one patient; IV levofloxacin 500 mg bid in one patient; IV ciprofloxacin 400 mg bid in two patients). A multidrug treatment was administered in three cases: fluoroquinolone + aminoglycoside in one patient; glycopeptides and cephalosporin in one case. In one case (infected with multiresistant *S. epidermidis* and *P. aeruginosa*), IV vancomycin 500 mg qid (followed by PO linezolid 600 mg bid), in combination with PO ciprofloxacin 750 mg bid were administered. Cleaning of external auditory canal was performed in all cases. The median duration of antibiotic treatment was 12.4 weeks (range, 8-20 weeks). No adverse effects were observed.

Two patients underwent biopsy; four patients underwent surgical treatment (debridement of EAC in three cases and facial nerve decompression in one other). No patient received hyperbaric oxygen therapy. All patients underwent serial suctions of ear secretion and, if necessary, removal of granulation tissue.

Histological examination was obtained in six cases, showing granulation tissue in all cases.

Outcome

Ten patients out of 11 experienced complete clinical recovery even if one patient had a residual facial palsy. One patient, despite 18 weeks of medical treatment and a surgical debridement, died of an infective skull base osteomyelitis with multiple nerve involvement caused by *P. aeruginosa* and *S. epidermidis*. In this case, an initial diagnostic delay of 16 weeks had been documented. Surgical treatment was carried out in another two patients.

At the end of treatment, mean ESR was 12.5 mm/h, mean CRP value 0.6 mg/l; mean WBC 6778 × 10^9/l.

CT scan at the end of treatment was performed in all patients (except for patient # 9 who died, and who had undergone other scans during treatment): persistent erosion of EAC was documented in 5/11 patients; TMJ involvement was shown in 2/11 cases; only one patient showed a persistent involvement of mastoid and middle ear; one patient presented signs of erosion of the skull base; the presence of soft tissue in EAC was revealed in one patient.

LeukoScan was performed in three patients at the end of treatment; a reduced tracer uptake in comparison with previous exam was found in two patients, and a persistent tracer uptake was found in one patient. The latter continued medical treatment until MEO was resolved on the basis of this imaging finding. The remaining 10 patients were followed-up for at least six months after the end of treatment. No recurrences were registered during follow-up period.

Discussion

Today, clinical management of MEO is still difficult and full in pitfalls. This is particularly important as early diagnosis is considered a major prognostic factor[8-10]. We propose a flow-chart which could guide physicians in the management of MEO (Figure 1).

In comparison with a previous one[1], our flow-chart suggests a possible assessment after 6-8 weeks of treatment, highlighting the usefulness of 99m Tc sulesomab. Ear-swab culture may not always be reflective of the pathogenic organism infecting the temporal bone in MEO. Tissue biopsy should be recommend in cases in which there is poor or no response to ear-swab culture-directed therapy[11].

In our series, even though the small number of cases does not allow us to reach statistically significant results, prognosis did not seem to be related to patients' age; this is in line with some studies[12, 13]. On the contrary, Soudry et al's results suggested a lower life expectancy for patients aged 70 years and older[14].

In our series, male/female ratio showed a higher percentage of male patients. Other authors have registered similar findings[15-17]. Explanations for this higher male incidence are hard to find. Nine of our patients were affected by diabetes, in line with some studies which report a prevalence of this disease in MEO of between 65% and 95%[12, 13, 17]. However, some papers have shown that degree of glucose intolerance and clinical outcome does not present a relevant correlation[12, 18]. Similarly, HbA1c levels were altered in just 3/11 of our cases. These three cases recovered fully with an average duration of treatment of 11.3 weeks, which was close to the

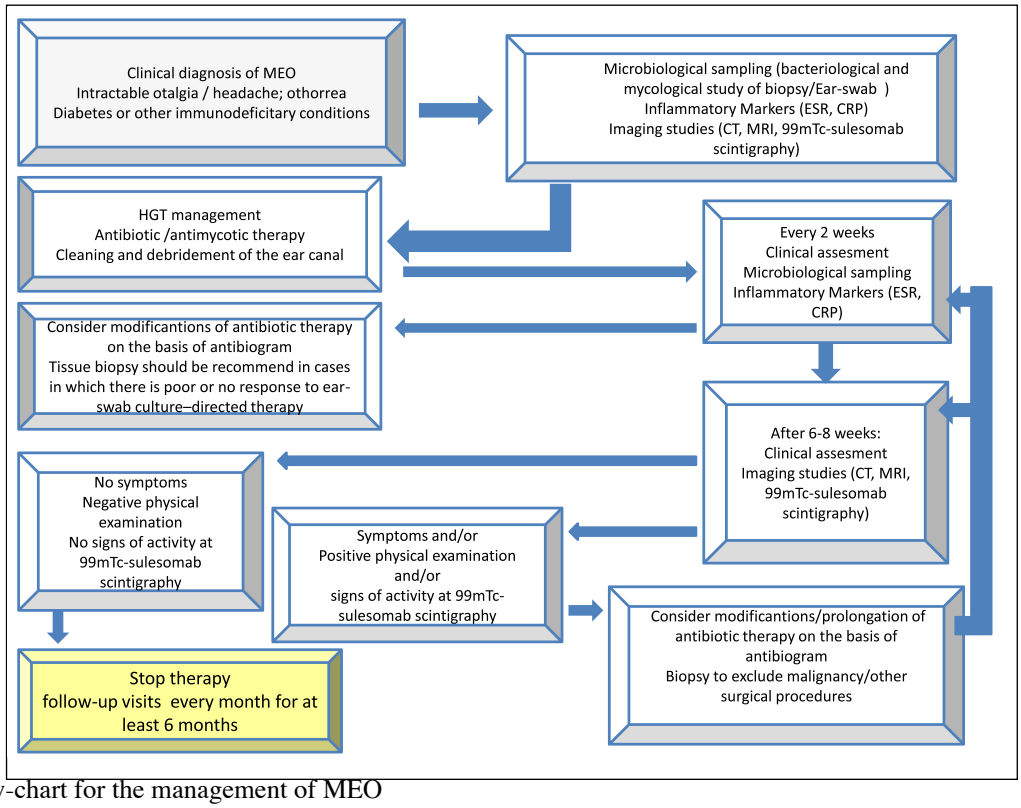

Fig. 1: Flow-chart for the management of MEO

general average (12.4 weeks). This finding supports the thesis of the weakness of this parameter as a prognostic index for MEO.

In our series, mean diagnostic delay was 12.4 weeks, longer than Loh et al's[12] results but between 1 and 7 months, as other studies report[19, 20].

Lethality was 1/11 in our series; in the series reported by Hariga et al[17] this was 0/19; in Jacobsen et al's series it was al 2/46[21], and in the series by Al-Noury et al, 0/18[22]. It is believed that mortality rate for MEO is not related to age, sex, degree of glucose tolerance, duration of diabetes, microorganism, comorbid condition, or involvement of a single cranial nerve. Instead, skull base osteomyelitis, intracranial extension, and involvement of multiple cranial nerves can be considered negative prognostic indexes[18]. The most involved cranial nerve in our series was the facial nerve, as other studies reported[1, 23].

Patients who had poorer outcomes presented a residual facial palsy in one case and a multiple cranial nerves involvement in one other case. These findings seem in line with other authors' experience[12-14, 18].

Recurrence rate in our series was 0/11. Al-Noury et al reported a recurrence rate of 3/18[22], Hariga et al. 3/19[17], and Jacobsen et al. 2/51[21].

A dramatic decrease of post-treatment CRP and ESR values in comparison with initial values was found in our series. However, to confirm the usefulness of these markers in the evaluation of disease activity serial readings are necessary[12].

Differential diagnosis of MEO includes: severe external otitis and temporal bone cancer. Histological examination may be necessary as it is the only definitive method to distinguish an invasive infection from malignancies[24-26].

CT findings in our series highlighted the involvement of EAC in all cases, in line with Peleg's work[27]. Erosion of the EAC was found in 9/11 patients; two patients did not present with this finding probably because referral to our department was more timely (diagnostic delay of 8 weeks in the first case, and 9 weeks in the second one): demineralization becomes evident after weeks of inflammation[1], making early disease hard to detect using CT scan.

Contrary to the observations by Peleg et al[27], but in line with other authors' works[12, 28], there was no correlation between the presence of major area involvement (TMJ, skull base, parotid space, etc) and poor outcome in our series.

CT scans at follow-up showed some persistent changes in clinically recovered patients, in line with other authors' experience[22]. These outcomes reinforced the following concept: once demineralization has occurred, bony changes persist even after inflammation has been resolved[1, 29] (Fig. 2). Thus, CT scan is not reliable in predicting disease activity[12, 28]. To evaluate MEO activity Gallium-67 citrate (Ga-67) scintigraphy can be used[30]. Ga-67 concentrates in areas of inflammation by binding directly to bacteria, and therefore can be used to follow the resolution of osteomyelitis and assess when antibiotic therapy can be stopped[30].

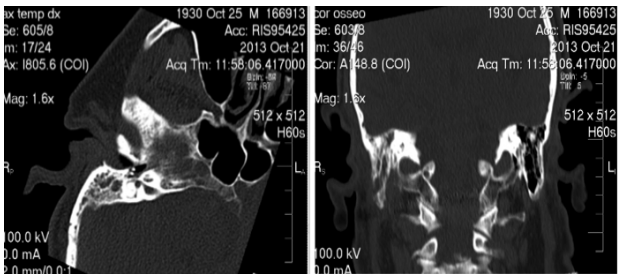

Fig. 2: Patient n. 1. Coronal and assial CT scan highlighting an osteitis of the right temporal bone.

In alternative to this technique, we opted for the use of Tc-sulesomab scan in three patients. This method would appear to be quite useful (Fig. 3). It allowed identification of a case where the disease still showed signs of activity thus requiring continuation of antibiotic treatment.

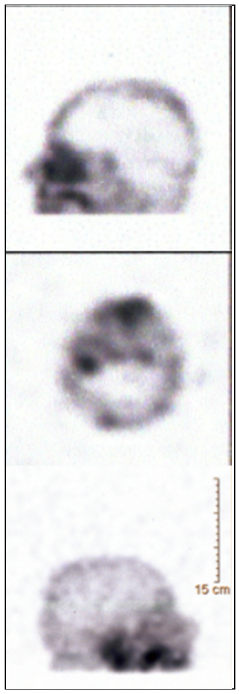

Fig. 3: Patient n. 1 "4h (at the top and in the middle) and 24h (at the bottom) 99mTc Sulesomab scans in an under-treatment patient affected by a MEO of the right ear. An uptake of the tracer is highlighted at the level of the right temporal bone".

In comparison with 67Ga scintigraphy, some advantages can be mentioned for 99mTc-sulesomab. It shows higher sensitivity and specificity in the evaluation of osteomyelitic processes, such as diabetic foot[31, 32]. Moreover, radiation dose is lower (effective dose 5-6 mSv) compared to 67Ga-Citrate (about 10 mSv)[31]. Finally, time of execution for a 99mTc-sulesomab

scan is shorter than for a 67Ga scintigraphy (4-24h vs. 48-72h)[33].

MRI may be useful to show nasopharyngeal, parapharyngeal, and/or intracranial involvement and TMJ infiltration[34]. In our series, patients who underwent an MRI scan presented with the involvement of one or more of the above structures, and this imaging examination was useful to evaluate the extension of the invasive process.

Another imaging technique that may be used in patients affected by MEO is Technetium-99m methyline diphosphonate (Tc-99m-MDP) bone scintigraphy. Tc-99m-MDP bone scintigraphy can be used in the initial evaluation of patients with suspected osteomyelitis as it demonstrates alterations in osteoblastic activity. However, bone scan remains positive for a long time after successful treatment of osteomyelitis due to the ongoing process of bone repair, so it should not be used to monitor evolution[35-37].

Fluoroquinolones were the most used antibiotics. The antipseudomonal activity of fluoroquinolones has made them the treatment of choice, although a combination of an aminoglycoside and beta-lactam antibiotic may also be quite effective[1, 38].

Average treatment duration in surviving patients of our series was 11.7 weeks. As reported in literature, treatment should be continued for at least 4 weeks, but the duration of therapy can be modified on the basis of clinical course, ESR, CRP and imaging findings[38]. Hyperbaric oxygen has been used with contrasting results by several authors and may be considered as an adjuvant treatment for refractory cases although efficacy remains doubtful[39-42].

Today, extensive surgical debridement is no longer considered the gold standard treatment and has been replaced by minimally invasive debridement associated with long-term antimicrobial chemotherapy[23, 27]. Further extension of the operation may promote the spread of infection to healthy bone[43]. Four patients of our series underwent surgery and two resulted in poor outcome, supporting the above considerations.

Conclusion

MEO still remains today a very challenging issue. Randomized clinical trials are needed to better clarify which medical and surgical treatment could be the gold standard. A consensus diagnostic flow diagram could help in the management of this pathology. The role of 99mTc-sulesomab as a rapid, effective and safe imaging agent for treatment evaluation and follow-up of patients with MEO deserves to be investigated.

References

1) Rubin Grandis J, Branstetter BFt, Yu VL *The changing face of malignant (necrotising) external otitis: clinical, radiological, and anatomic correlations*. Lancet Infect Dis 2004; 4: *34-39*.
2) Yang TH, Kuo ST, Young YH *Necrotizing external otitis in a patient caused by Klebsiella pneumoniae*. Eur Arch Otorhinolaryngol 2006; 263: *344-346*.
3) Carfrae MJ, Kesser BW *Malignant otitis externa*. Otolaryngol Clin North Am 2008; 41: *537-549*, viii-ix.
4) Joshua BZ, Sulkes J, Raveh E, Bishara J, Nageris BI *Predicting outcome of malignant external otitis*. Otol Neurotol 2008; 29: *339-343*.
5) Chandler JR *Malignant external otitis*. Laryngoscope 1968; 78: *1257-1294*.
6) Pacini DL, Trevorrow T, Rao MK, Birck HG, *Barson WJ Malignant external otitis as the presentation of childhood acute lymphocytic leukemia*. Pediatr Infect Dis J 1996; 15: *1132-1134*.
7) Cohen D, Friedman P *The diagnostic criteria of malignant external otitis*. J Laryngol Otol 1987; 101: *216-221*.
8) Soudry E, Joshua BZ, Sulkes J, Nageris BI *Characteristics and prognosis of malignant external otitis with facial paralysis*. Arch Otolaryngol Head Neck Surg 2007; 133: *1002-1004*.
9) Grandis JR, Curtin HD, Yu VL *Necrotizing (malignant) external otitis: prospective comparison of CT and MR imaging in diagnosis and follow-up*. Radiology 1995; 196: *499-504*.
10) Mahdyoun P, Pulcini C, Gahide I, et al. *Necrotizing otitis externa: a systematic review*. Otol Neurotol 2013; 34: *620-629*.
11) Hobson CE, Moy JD, Byers KE, et al. *Malignant Otitis Externa: Evolving Pathogens and Implications for Diagnosis and Treatment*. Otolaryngol Head Neck Surg 2014.
12) Loh S, Loh WS *Malignant otitis externa: an Asian perspective on treatment outcomes and prognostic factors*. Otolaryngol Head Neck Surg 2013; 148: *991-996*.
13) Franco-Vidal V, Blanchet H, Bebear C, Dutronc H, Darrouzet V *Necrotizing external otitis: a report of 46 cases*. Otol Neurotol 2007; 28: *771-773*.
14) Soudry E, Hamzany Y, Preis M, et al. *Malignant external otitis: analysis of severe cases*. Otolaryngol Head Neck Surg 2011; 144: *758-762*.
15) Chen YA, Chan KC, Chen CK, Wu CM *Differential diagnosis and treatments of necrotizing otitis externa: a report of 19 cases*. Auris Nasus Larynx 2011; 38: *666-670*.
16) Guevara N, Mahdyoun P, Pulcini C, et al. *Initial management of necrotizing external otitis: errors to avoid*. Eur Ann Otorhinolaryngol Head Neck Dis 2013; 130: *115-121*.
17) Hariga I, Mardassi A, Belhaj Younes F, et al.

Necrotizing otitis externa: 19 cases' report. Eur Arch Otorhinolaryngol 2010; 267: *1193-1198*.

18) Chen CN, Chen YS, Yeh TH, Hsu CJ, Tseng FY *Outcomes of malignant external otitis: survival vs mortality*. Acta Otolaryngol 2010; 130: *89-94*.

19) Lee S, Hooper R, Fuller A, et al. *Otogenic cranial base osteomyelitis: a proposed prognosis-based system for disease classification*. Otol Neurotol 2008; 29: *666-672*.

20) Jacobsen LM, Antonelli PJ *Errors in the diagnosis and management of necrotizing otitis externa*. Otolaryngol Head Neck Surg 2010; 143: *506-509*.

21) Jacobsen LM, Antonelli PJ *Errors in the diagnosis and management of necrotizing otitis externa*. Laryngoscope 2010; 120 Suppl 4: *S207*.

22) Al-Noury K, Lotfy A *Computed tomography and magnetic resonance imaging findings before and after treatment of patients with malignant external otitis*. Eur Arch Otorhinolaryngol 2011; 268: *1727-1734*.

23) Omran AA, El Garem HF, Al Alem RK *Recurrent malignant otitis externa: management and outcome*. Eur Arch Otorhinolaryngol 2012; 269: *807-811*.

24) Devaney KO, Boschman CR, Willard SC, Ferlito A, Rinaldo A *Tumours of the external ear and temporal bone*. Lancet Oncol 2005; 6: *411-420*.

25) Mattucci KF, Setzen M, Galantich P *Necrotizing otitis externa occurring concurrently with epidermoid carcinoma*. Laryngoscope 1986; 96: *264-266*.

26) Grandis JR, Hirsch BE, Yu VL *Simultaneous presentation of malignant external otitis and temporal bone cancer*. Arch Otolaryngol Head Neck Surg 1993; 119: *687-689*.

27) Peleg U, Perez R, Raveh D, Berelowitz D, Cohen D *Stratification for malignant external otitis*. Otolaryngol Head Neck Surg 2007; 137: *301-305*.

28) Sudhoff H, Rajagopal S, Mani N, et al. *Usefulness of CT scans in malignant external otitis: effective tool for the diagnosis, but of limited value in predicting outcome*. Eur Arch Otorhinolaryngol 2008; 265: *53-56*.

29) Rubin J, Yu VL, Stool SE *Malignant external otitis in children*. J Pediatr 1988; 113: *965-970*.

30) Stokkel MP, Boot CN, van Eck-Smit BL *SPECT gallium scintigraphy in malignant external otitis: initial staging and follow-up*. Case reports. Laryngoscope 1996; 106: *338-340*.

31) Delcourt A, Huglo D, Prangere T, et al. *Comparison between Leukoscan (Sulesomab) and Gallium-67 for the diagnosis of osteomyelitis in the diabetic foot*. Diabetes Metab 2005; 31: *125-133*.

32) Galletti F, Cammaroto G, Galletti B, et al. *Technetium-99m (Tc)-labelled sulesomab in the management of malignant external otitis: is there any role?* Eur Arch Otorhinolaryngol 2014.

33) Boerman OC, Rennen H, Oyen WJ, Corstens FH *Radiopharmaceuticals to image infection and inflammation*. Semin Nucl Med 2001; 31: *286-295*.

34) Kwon BJ, Han MH, Oh SH, Song JJ, Chang KH MRI findings and spreading patterns of necrotizing external otitis: is a poor outcome predictable? Clin Radiol 2006; 61: 495-504.

35) Parisier SC, Lucente FE, Som PM, et al. *Nuclear scanning in necrotizing progressive "malignant" external otitis*. Laryngoscope 1982; 92: *1016-1019*.

36) Weber PC, Seabold JE, Graham SM, et al. *Evaluation of temporal and facial osteomyelitis by simultaneous In-WBC/Tc-99m-MDP bone SPECT scintigraphy and computed tomography scan*. Otolaryngol Head Neck Surg 1995; 113: *36-41*.

37) Sreepada GS, Kwartler JA *Skull base osteomyelitis secondary to malignant otitis externa*. Curr Opin Otolaryngol Head Neck Surg 2003; 11: *316-323*.

38) Rubin J, Yu VL *Malignant external otitis: insights into pathogenesis, clinical manifestations, diagnosis, and therapy*. Am J Med 1988; 85: *391-398*.

39) Lucente FE, Parisier SC, Som PM *Complications of the treatment of malignant external otitis*. Laryngoscope 1983; 93: *279-281*.

40) Lucente FE, Parisier SC, Som PM, Arnold LM *Malignant external otitis: a dangerous misnomer?* Otolaryngol Head Neck Surg 1982; 90: *266-269*.

41) Mader JT, Love JT Malignant external otitis. *Cure with adjunctive hyperbaric oxygen therapy*. Arch Otolaryngol 1982; 108: *38-40*.

42) Davis JC, Gates GA, Lerner C, et al. *Adjuvant hyperbaric oxygen in malignant external otitis*. Arch Otolaryngol Head Neck Surg 1992; 118: *89-93*.

43) Mardinger O, Rosen D, Minkow B, et al. *Temporomandibular joint involvement in malignant external otitis*. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2003; 96: *398-403*.

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