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Original Study

Malignant Otitis Externa: How to Monitor the Disease in Outcome Estimation?

Malign Otitis Eksterna: Hastalığın Sonlanımının Tahmine Yönelik Takibi

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ABSTRACT

Objective: *Malignant otitis externa (MOE) is a serious disease affecting mainly the elderly diabetic patients that may result in mortality. It was aimed to evaluate the relationship between treatment responses and clinical and radiologic parameters among progress of the disease. Secondary aim was to present our clinical outcomes in the treatment of malignant otitis externa.*
Method: *This study was retrospectively conducted in a single center. Reviewed data included history of complaints, duration of symptoms, addition of hyperbaric oxygen treatment, presence of surgical intervention, pathological findings, culture positivity and microorganism, laboratory findings, scintigraphy, imaging modalities and outcome of disease.*
Result: *A total of 26 cases with malignant external otitis including 17 females (65.4%) and nine males (34.6%) patients were included in our study. Duration of symptoms before the initiation of treatment, and hyperbaric oxygen treatment did not positively influence the outcome. Inflammatory markers and Peleg staging significantly reflected the treatment response.*
Conclusion: *Close monitoring of inflammatory parameters is the key point in the prediction of prognosis. Planning the management and predicting the outcomes rely on proper radiological and clinical assessment of the extent of disease. In the assessment of MOE, universal scoring systems should be preferred for pooling the data in comparable manner.*

Keywords: *Otitis externa, malignant; osteomyelitis, skull-base, otorrhea, outcome prediction*

ÖZ

Amaç: *Malign otitis eksterna esas olarak yaşlı diyabetik hastaları etkileyen ve ölümle sonuçlanabilen ciddi bir hastalıktır. Hastalığın ilerleyişi arasında tedavi yanıtları ile klinik ve radyolojik parametreler arasındaki ilişkinin değerlendirilmesi amaçlandı. İkincil amaç, malign otitis eksterna tedavisinde klinik sonuçlarımızı sunmaktı.*
Yöntem: *Retrospektif olarak tek merkezde yapıldı. İncelenen veriler arasında şikayet öyküsü, semptomların süresi, hiperbarik oksijen tedavisi eklenmesi, cerrahi girişim varlığı, patolojik bulgular, kültür pozitifliği ve mikroorganizma, laboratuvar bulguları, sintigrafi, görüntüleme yöntemleri ve hastalığın sonucu yer aldı.*
Bulgular: *Çalışmamıza 17 kadın (%65,4) ve 9 erkek (%34,6) olmak üzere toplam 26 malign eksternal otitisli hasta dahil edildi. Tedaviye başlamadan önce semptom süresi, Hiperbarik oksijen tedavisi sonucu olumlu etkilemedi. Enflamatuar belirteçler ve Peleg evreleme, tedavi yanıtını önemli ölçüde yansıtıyordu.*
Sonuç: *Enflamatuar parametrelerin yakından izlenmesi prognoz tahmininde anahtar noktadır. Yönetimin planlanması ve sonuçların tahmin edilmesi, hastalığın derecesinin uygun radyolojik ve klinik değerlendirmesine dayanır. MOE değerlendirmesinde, verilerin karşılaştırılabilir bir şekilde havuzlanması için evrensel puanlama sistemleri tercih edilmelidir.*

Anahtar kelimeler: *Malign otitis eksterna, kafa tabanı osteomyeliti, otore, tedavi sonlanımı*

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INTRODUCTION

Malignant (necrotizing) otitis externa (MOE), or skull base osteomyelitis is an aggressive form of skin infection of the external ear with possibility to spread to the temporal bone[1].

Patients present with severe otalgia, otorrhea that are frequently unresponsive to treatment, impaired hearing, and granulations. Cranial nerve involvement is frequent in MOE with the involvement of the seventh cranial nerve which is the most commonly affected one, but the lower cranial nerves can also be affected[2].

Cohen et al.[3] defined the diagnostic criteria to describe the severity of disease. Otorrhea, otalgia, edema, microabscesses, granulation tissue, failure to response to treatment after more than a week are amongst the major criteria. All major criteria should be present to confirm the diagnosis.

Failure to respond to 1 to 3 weeks of trial of intensive local and systemic treatment clarifies the diagnosis in challenging cases[4]. The primary treatment of MOE is long-term antimicrobial therapy for at least six weeks with anti-pseudomonal antibiotics and topical therapy with frequent suctioning and aural toilette. Surgical interventions with multiple local debridement of necrotic tissue and addition of hyperbaric oxygen therapy (HBOT) are considered in appropriate cases[4].

Recently, the best imaging modality for diagnosing and assessing the treatment response in MOE has been a point of concern regarding the accuracy and cost-effectiveness[5].

We aimed to evaluate the relationship between treatment responses and clinical and radiologic parameters effective in the progress of the disease. Secondary aim was to present our clinical outcomes in the treatment of malignant otitis externa.

MATERIALS AND METHODS

Study population and recruitment

This is a retrospective study which was conducted in a single center.

The study was approved by the local ethical committee with decision no of 2238. Informed consent was not obtained due to the retrospective nature of the study.

Medical records between January 2010-March 2020 containing data related to the history of complaints, duration of symptoms, duration and content of treatment, addition of HBOT to the treatment regimen, presence of surgical intervention, pathological findings, culture positivity and microorganisms, laboratory findings, scintigraphy and imaging modalities including both computed tomography (CT) and magnetic resonance imaging (MRI) were collected. Outcomes of disease and presence of cranial neuropathy of patients who were diagnosed with MOE were reviewed. Findings were recorded along with comorbidities for each case. Reviewed records contained data related to laboratory, radiologic and Technesium-99 scintigraphic imaging obtained before the initiation of treatment and after completion of treatment before discharge. Scintigraphic imaging was performed at three hours after Tc- 99m MDP injection. The dose of the radiopharmaceutical agent was adjusted for the size of the patient. The imaging was acquired by a dual-head SPECT-CT Gamma Camera (SymbiaIntevo Excel; Siemens AG, Erlangen, Germany) with a low-energy, high-resolution collimator in our nuclear medicine department.

Diagnosis of malignant otitis externa was made according to the criteria of Cohen and Friedman as follows: positive findings on CT scan of the temporal bone, presence of exudative drainage or granulation tissue in the external auditory canal (EAC), clinical findings of otalgia, edema, failure of local treatment after more than a week, histo-

logical exclusion of other causes with same symptomatology like malignancies and cholesteatomas, and presence of micro-abscesses on pathological samples obtained during surgery. Patients were staged according to the CT findings as stated by Peleg[6] (Table 1). Time interval between the onset of the first symptom and initiation of the treatment was prolonged. Therefore, we defined early, and late treatment if this time interval was less or more than three months, respectively.

Predictors of treatment response were defined as age and sex of the patient, comorbidity, presence of cranial neuropathy, length of inpatient treatment, length of treatment (LOT), duration of symptoms (DOS) that is the time interval between the onset of the first symptom and initiation of the treatment and inflammatory findings[7]. In cases with diabetes mellitus HbA1c and fasting blood glucose levels were also analyzed.

Outcome measures were defined as follows: DOD (died of disease), DOC (died of other causes), NED (No evidence of disease), AWD (alive but with refractory disease meaning incomplete resolution of symptoms).

Clinicopathological grading system defined by Carney et al was used accordingly: stage 1: clinical evidence of malignant otitis externa with infection of soft tissues beyond the EAC, but negative Tc-99m bone scan; stage 2: Soft tissue infection beyond the EAC with positive Tc-9m9 bone scan; stage 3 a/b: as above, but with cranial nerve paralysis as single/multiple respectively; stage 4: meningitis, empyema, sinus thrombosis or brain abscess[8]. Peleg scoring and Carney staging were calculated before the initiation of treatment and after completion of treatment in advance of discharge.

Statistical Analysis

Normal distribution of data was checked with Kolmogorov-Smirnov and Shapiro-Wilk tests. The statistical significance level was set at <0.05. The differences between the groups were compared using a chi-Square and Fisher's exact tests. The findings were statistically analyzed with SPSS for Windows, version 16.0 (SPSS Inc., Chicago, Ill., USA).

RESULTS

A total of 26 patients with malignant external otitis, including 17 female (65.4%) and 9 male (34.6%) patients were enrolled in our study. The mean age of the cases was 67.27±10.59 years (range: 47-85 years); 76.9% (n:20) of them were 60 years old and above, 23.1% (n:6) of them were under 60 years old. Right ear was affected in 38.5% (n:10), and left ear in 46.2% (n:12) of the cases and bilateral involvement was found in 15.4% (n:4) of the patients. While ear pain and

Table 1. Peleg CT severity score.

	Group 1 (n:10)			
Area	**0**	**1**	**2**	**3**
External Ear canal	No involvement (NI)	Mild thickening	Moderate thickening	Passage closed
Mastoid	NI	Mucosal thickening	Fluid & air	Almost full
Middle ear	NI	Mucosal thickening	Fluid & air	Almost full
Nasopharynx	NI	Mild asymmetry / eustachian tube is open	Mild asymmetry / eustachian tube is closed	Severe asymmetry
Parotid gland	NI	Mild swelling and infiltration	Severe swelling and infiltration	-
Temporal bone	NI	Bone destruction	-	-
Temporomandibular joint	NI	Enlarged joint space	Bone destruction	-
Skull base	NI	Bone destruction	-	-

purulent ear discharge were observed in 88.5% of the patients (n:23) at the time of diagnosis, peripheral facial paralysis was observed in addition to ear pain and ear discharge in 3 patients (11.5%). When the pathology results were evaluated; Aspergillosis was reported in one (3.8%) case, while chronic inflammation was found in 96.2% (n:25) of the cases. Distribution of comorbidities and culture of ear discharge at the time of diagnosis were presented in Tables 2 and 3.

Table 2. Imaging methods used at the time of diagnosis.

	n	%
CT	4	15.4
CT+MR	7	26.9
CT+SCINT	3	11.5
MR+CT+SCINT	12	46.2

Table 3. Distribution of comorbidity at the time of diagnosis.

	n	%
1	11	42.3
1+2	2	7.7
1+2+12	1	3.8
1+2+3+10	1	3.8
1+2+3+13	1	3.8
1+2+3+6+13	1	3.8
1+2+8+11	1	3.8
1+3	3	11.5
1+3+10	1	3.8
1+3+10+13	1	3.8
1+4	1	3.8
1+5	1	3.8
9	1	3.8

DM:1, HT:2, IHD:3, HEARING AID: 4 HEMATOLOGICAL MALIGNANCY: 5 THYROIDITIS: 6, HYPERLIPIDEMIA: 7 GLOCOMA: 8 BPH: 9 NEPHROPATHY: 10, AMPUTATION: 11, COPD: 12 CABG: 13

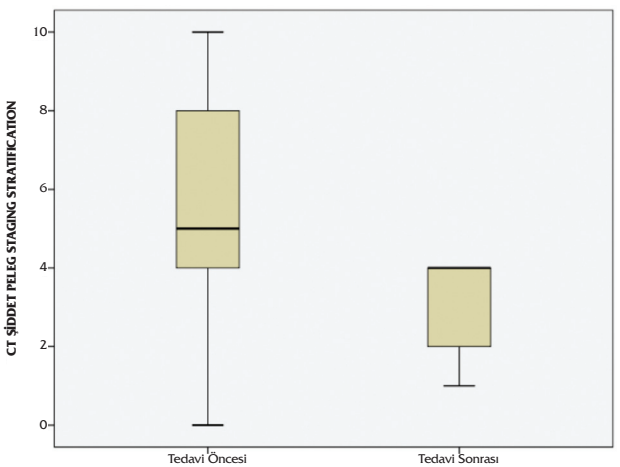
Conservative treatments were initiated by the time of diagnosis. Broad spectrum antibiotics in combination were prescribed to the patients. Antibiotic regimen was switched according to the culture results. According to the imaging findings, extention of disease was identified. Microscopic examination of ear canal was performed daily. Drainage character and amount together with the condition of the tympanic membrane and patient's pain perception were recorded. In case of suspicion for refractory disease surgical intervention was considered. If the case was not suitable for surgical intervention at first attempt or disease was not localized HBOT was added on to the treatment. Nine patients underwent surgical intervention, five of them had radical mastoidectomy and four of them had subtotal petrosectomy. Two patients who had undergone surgical intervention with radical mastoidectomy, died of the disease.

The most common microorganism in the culture samples taken from the EAC of the patients was *Pseudomonas aeruginosa* with a rate of 61.5% (n=16); This was followed by skin flora bacteria with 11.5% (n=3) and *Coagulase Negative Staphylococcus* with 7.7% (n=2) (Table 4). The mean duration of the disease was calculated as 2.92±2.39 (range=1-12) months and the mean treatment duration was 51.50±38.01 (range=14-159) days; while 34.6% (n=9) of the patients

Table 4. Culture results.

	n	%
Pseudomonas aeruginosa	16	61.5
Coagulase Negative Staphylococcus	2	7.7
Candida	1	3.8
Aspergillus spp.	1	3.8
Skin flora	3	11.5
Escherichia coli	1	3.8
GR - bacillus	1	3.8
Pseudomonas aeruginosa + Candida albicans	1	3.8

Table 5. Peleg staging before and after treatment.



come measures with HBOT status and the duration before the initiation of the treatment (p=0.870 and p=0.991, respectively). HBOT was applied under 2.5 ATA (atmospheric absolute pressure) for 20 sessions. The HBOT sessions consisted of 10 min of compression to 2.5 ATA, 60 min. at 2.5 ATA and 10 min of decompression.

Table 6. Mean PELEG and CARNEY scores of outcome measures.

OUTCOME	n	CARNEY score	PELEG score
DOC	2	2.5	6
DOD	7	2.71	5.3
AWD	4	2.5	6.3
NED	12	2.5	5.2

Table 7. Comparison of laboratory results before and after treatment.

	Before treatment (Mean±SS)	After treatment (Mean±SS)	P value
ESR (mm/h)	56.35±30.37	42.92±27.90	0.018*
CRP (mg/L)	17.79±37.68	11.86±42.95	0.036*
WBC (x10^6/L)	10.54±16.31	7.17±2.27	0.243
N/L	3.98±2.81	4.19±6.44	0.101
PLT (x10^9/L)	275.65±109.00	227.23±78.58	0.004*
HBA1c (%)	7.60±2.23	7.09±2.12	0.073
Glucose (mg/dL)	177.48±66.58	163.54±77.74	0.300
Peleg Staging	5.04±2.94	3.25±1.18	0.040*

**= p<0.05 statistically significant.*

The laboratory findings of our patients before and after the treatment were compared; Mean erythrocyte sedimentation rate (ESR) before treatment (56.35±30.37 mm/hr), CRP (17.79±37.68 mg/L) and platelet counts (275.65±109.00x10^9/L) values after treatment (42.92±27.90x10^9/L), CRP (11.86±42.95 mg/L) and platelet counts (227.23±78.58x10^9/L) values were found to be significantly higher (p=0.018, 0.036 and 0.004, respectively). In addition, the mean Peleg staging score before treatment (5.04±2.94) was found significantly higher than the post-treatment mean Peleg staging score (3.25±1.18) (p=0.040).

In our study, 61.5% (n=16) of cases showed increased uptake in the pre-treatment scintigraphy, while this rate was determined as 30.8% (n=8) after the treatment. Follow-up scintigraphy of 10 patients with pretreatment involvement became negative after treatment. No statistically significant difference was observed in the pre- and post-treatment scintighraphic evaluations. Magnetic resonance imaging was performed after the treatment, and it was found that 11.5% of the cases (n=3) had no signs of inflammation, and the pathology continued in 53.8% (n=14) of the cases.

DISCUSSION

Malignant otitis externa is a progressive, invasive and infective disease of the external auditory canal the disease usually occurs in diabetic patients affected by microangiopathic changes. Although *Pseudomonas aeruginosa* is the most common agent, *Aspergillus fumigatus* and other organisms may also be causative agents in immunocompromised patients[9]. Immunodeficiency predisposes to this disease and suppresses the symptoms of infection. Granulation tissue that occurs in MOE can mimic malignancy and a biopsy should be performed. The agents are bacteria such as methicillin-resistant *Staphylococcus aureus (MRSA)*, *Klebsiella* and *Proteus mirabilis* or fungal agents such as *Aspergillus* and *Candida*. However, *Pseudomonas aeruginosa* is the leading pathogen especially in immunocompromised patients with comorbidities such as diabetes, HIV and hematological diseases[5,10]. The most common microorganism in the culture samples taken from the external auditory canal of the patients was *Pseudomonas aeruginosa* in accordance with literature[10,11].

The duration between the first symptom and initiation of treatment was shown to be a promising parameter for the prediction of prognosis[3], however in our study a significant association could not be determined in our study. As the case distribution among the groups formed based on outcome measures were not similar, prognosis

analysis was not performed for most of the parameters reviewed. This can be considered as the weak side of the study.

Microangiopathy of small vessels is the main mechanism in tissue damage resulting in necrosis. The venous circulation causes the infection to spread to the dural sinuses and extend intracranially[11]. Although several studies are available in favor of HBOT in the treatment process of MOE[12,13], we did not find any significant difference between HBOT status and Carney stages and disease outcomes. The treatment of these patients is difficult due to the difficulty of surgical access to the skull base and its proximity to vital structures. In addition, necrotic changes in the bone limit the effectiveness of antibiotics.

Imaging methods include CT, MRI and radionuclide scintigraphy. The delay in the clinical response to be reflected in the imaging modalities, limits the role of imaging in the follow-up[14]. Lee et al.[7] investigated 38 patients with malignant otitis externa to investigate the prognostic factors affecting the treatment outcomes. They determined survival predictors such as single Photon Emission Computerized Tomography (SPECT) stage, fungal infections, Charlson score, immunodeficiency status and cranial neuropathy. The SPECT-based staging system properly predicted the long-term outcome in these patients. In our results, there was a relationship between CT/scintigraphy and the treatment outcomes.

The combination of radiological and scintigraphy evaluations plays a very important role in the diagnosis and follow-up of patients and Tc-99m MDP is widely used in SPECT scanning as the first evaluation. Gallium scintigraphy may be useful in making a decision to terminate antibiotic therapy. However, it can be used even in the first evaluation. However, Tc-99m MDP SPECT/CT scanning is more cost-effective than gallium scanning[15]. In our study, the disease outcomes correlated with the predefined disease classification scores based on imaging and scintigraphy[6,8]. Filippi and Schillaci reported 100% sensitivity and 78% specificity of SPECT in detecting the infective focus[16]. Specificity increases when SPECT and CT findings are combined. SPECT/CT can detect the disease 24 to 48 hours after the bone anomaly occurs. A reliable differential diagnosis between severe external otitis and malignant external otitis can be made with the help of SPECT.

Inflammatory markers such as ESR, CRP, and platelet count were found as the main parameters in evaluating the treatment response, which is also consistent with the Peleg staging[6]. Appropriate evaluation for the prevalence MOE is very important for the treatment and prediction of the outcome. Early diagnosis leads to early treatment and improves prognosis.

CONCLUSION

Malignant otitis externa is a serious disease that usually affects elderly diabetic patients and other immunocompromised patients. Close monitoring of inflammatory parameters is the main factor in determining prognosis. Planning treatment management and predicting outcome depends on clinical evaluation and proper radiological evaluation. In the assessment of MOE universal scoring systems should be preferred for pooling the data in comparable manner.

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