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RESEARCH ARTICLE
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Impact of Hyberbaric Oxygen Therapy on Olfactory Function and Bulb Volume in Diabetic Patients with Olfactory Dysfunction

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ABSTRACT

Objective: Investigating the efficiency of Hyperbaric Oxygen Therapy (HBOT), recommended adjuvant therapy for diabetic neuropathy patients, in changing olfactory bulb volume and function in diabetic patients with olfactory dysfunction.
Materials and methods: 12 individuals, from a pool of type-2 diabetes mellitus (DM) patients with diabetic foot, had olfactory dysfunction based on olfaction test results. Olfactory tests and Magnetic Resonance Imaging (MRI) were used to measure and evaluate olfactory bulb volume and function changes in response to HBOT in these 12 patients (comparing Group 1 to Group 2). Similar analysis was carried out to compare the findings to those of 13 healthy patients (Group 3).
Results: Patients in Group 1, 2, and 3 were categorized as moderately hyposmic, mildly hyposmic, and normosmic, respectively based on olfaction test results. HBO treatment seems to be efficient as the OBV values and olfaction test results of Group 1 were significantly lower than those of Group 2. Comparison of olfactory tests shows statistically significant improvement in post-treatment odor perception.
Conclusion: It has been shown that both olfactory function and OB volumes based on MRI have increased significantly after HBO therapy in diabetic patients with olfactory dysfunction.

Keywords: Diabetes, anosmia, hyposmia, hyperbaric oxygen therapy, olfactory bulb volume

INTRODUCTION

The incidence of type-2 diabetes mellitus (DM) is gradually increasing, related to increased DM-associated morbidity and complication incidence. Decreased sense of smell is a major global health problem leading to reduced quality of life in affected individuals. The sense of smell presents crucial data about the surrounding and also takes part in the maintenance of protection and survival, feeding, social life, and sexuality (1).

Diabetic neuropathy, nephropathy and retinopathy are well-established complications of DM, but few studies have been conducted on the outcome of dysglycemia on the olfactory system. DM, in particular, can cause serious micro- and macrovascular complications that are related with significant morbidity, low life quality, shortened expectancy of life, and high cost of health services. The inititation and advance of DM complications are highly associated with injury to the renal glomeruli, peripheral nerves and retina, caused by dysglycemia and oxidative stress (2). Visual system is well-known to be affected by DM presence; however, there is inadequate data on the effect of DM on other sensory systems, such as olfaction. Patients with DM showed olfactory dysfunction, but its etiology is unclear (3).

It has also been suggested that olfactory function screening can be used as an early indicator of the existance of diabetic microvascular complications, like diabetic neuropathy (4).

While cranial neuropathies are often too rare, their association with diabetic neuropathy has been established very clearly. The frequency of cranial nerve involvement in patients with DM is

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reported to be 1% (5). Depending on the effect on the olfactory nerve, olfactory dysfunction may develop in DM. This can be considered as a sign of central neuropathy. It has been proven that olfactory dysfunction is related with diabetic neuropathy and peripheral retinopathy (6).

Hyperbaric Oxygen (HBO) rises, collagen production, angiogenesis and fibroblast proliferation improve tissue hypoxia and tissue perfusion, while reducing edema and inflammation. Systemic HBO therapy is proposed for the treatment of diabetic neuropathies (7).

The aim of study is to examine whether there is a change in olfactory function and olfactory bulb volume (OBV) after HBO therapy in patients with diabetic olfactopathy.

MATERIAL AND METHODS

Ethics approval was acquired from the local Research Ethics Committee before the study (Date: 07.10.2020, No: 2/2020.K-067). All individuals in this study were given a written informed consent for participation. This work was done in accordance with the rules of the Declaration of Helsinki.

Patients

Participants of the study were informed about the study, and they voluntarily signed the written consent forms. Demographic information of patients and healthy participants were recorded. 94 type-2 DM patients with diabetic foot who were followed up by the Internal Medicine Clinic took olfaction test. Only 12 patients were diagnosed diabetic olfactopathy and were included in our first group (Group 1). The second group in our study (Group 2) consists of the same 12 patients, who returned for control after receiving 30 sessions of HBO therapy. Finally, healthy volunteers were included in Group 3.

Evaluation of olfaction

To evaluate the olfactory function in the participants, the Connecticut Chemosensory Clinical Research Center (CCCRC) orthonasal olfaction test, for which validity and reliability in Turkish language were proven, was used. The CCCRC test consists of the n-butanol odor threshold test and the odor identification test. Detailed data on these tests has been provided in former studies (8). Olfactory tests were performed individually, and the maximum score was 7 (0: worst, 7: best olfaction), and the average score was calculated as the total CCCRC test score. According to the CCCRC orthonasal test, the scores were grouped as shown in Table 1.

Other causes of olfactory dysfunction in all participants of these three groups were examined in detail. Patients with other pathologies like inflammatory diseases were excluded from the study.

The standard treatment was designed with HBO therapy applied at a maximum atmospheres of absolute pressure (ATA) of 20 atm using a 10 m^3 volume single pressure chamber (Patterson Companies, Inc., St. Paul, MN, USA). The treatment consisted of two or three ATA for 90 minutes. The treatment was applied as two sessions per day, then one session the next day, and alternated during the therapy period which typically extended for 20 to 30 days. HBO treatment was evaluated clinically considering the duration of the therapy, expenses, contraindications, and complications. Contraindications include ocular aneurysm, lung disorders associated with risk of pneumothorax, high blood pressure, claustrophobia, convulsion due to oxygen toxicity, and rupture of the eardrum (9).

Magnetic Resonance Imaging (MRI) of Olfactory Bulb Volume (OBV)

OBV measurements were performed with a General Electric Signa MRI device using an 8-channel head coil. For OBV measurements, coronal T2-weighted three-dimensional turbo spin-echo (TSE) images were taken with a 2 mm section thickness and without section gap (gap=0). OBV values were evaluated by an experienced radiologist, and a double-blind technique was used on both sides via manual segmentation. OBV values were calculated in cubic millimeters (mm^3) (10) (Figure 1).

Statistical analyses

The data was analyzed using the MedCalc® v11.4.4 software. Mann Whitney U test was used to evaluate the effect of treatment,

Table 1: Classification of olfactory function according to CCCRC test

	Score Ranges
Anosmia	0-1.75
Severe hyposmia	2-3.75
Moderate hyposmia	4-4.75
Mild hyposmia	5-5.75
Normosmia	6-7

CCCRC: Connecticut Chemosensory Clinical Research Center test score

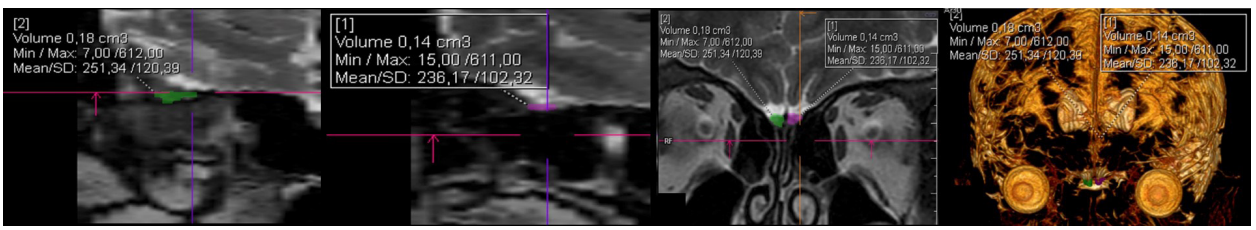

Figure 1: 44-year-old male diabetic patient with olfactory dysfunction before HBO treatment. Three-dimensional volume measurements of the bilateral olfactory bulbs: 140 mm^3 on the left side, 180 mm^3 on the right side. Right olfactory bulb, sagittal T2W MRI; Left olfactory bulb, sagittal T2W MRI; Bilateral olfactory bulbs, coronal T2W MRI; Bilateral olfactory bulbs, three-dimensional (3D) Volume rendering (VR) T2W MRI, respectively.

comparing the two dependent groups (Group 1 to Group 2), while we used the Kruskal Wallis to compare all three groups. A p-value of less than 0.05 was considered statistically significant.

RESULTS

The mean ± standard deviation of the patients' ages were 54.16±3.21 years and 55.23±4.22 years in Groups 1 and 2, respectively. Treatment groups (Groups 1 and 2) contained 10 male and two female participants, while Group 3 contained 11 male and two female participants. No statistically significant difference was found between the groups in terms of age and gender. Total mean ± standard deviation of CCCRC scores was 4±0.71 in Group 1, 5.08±0.70 in Group 2, and 6.42±0.31 in Group 3; the scores differed significantly among the groups. The mean CCCRC scores in Group 1, Group 2, and Group 3 were adequately hyposmic, mildly hyposmic, and normosmic. Figure 2 and Figure 3 show boxplots of the CCCRC scores and OBV of pre-treatment patients, post-treatment patients, and healthy individuals, respectively. Average ± standard deviation of OBV values was 60.08±5.35 mm^3 in Group 1, 71.29±6.55 mm^3 in Group 2, and 76.46±11.36 mm^3 in Group 3. OBV values and CCCRC test scores of Group 1 were significantly lower than those of Group 3 (both p-values<0.01). When Group 1 and Group 2 were compared, a statistically significant increase was observed in OB volumes following HBO treatment.

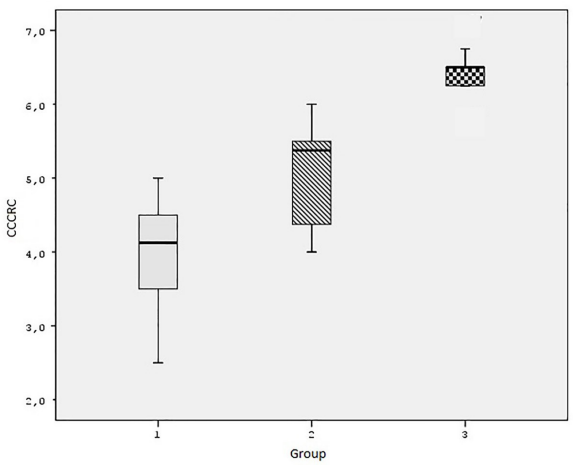

Figure 2: Boxplots for CCCRC scores of the groups of pre-treatment patients, post-treatment patients, and healthy individuals.

In Group 1, three patients were severely hyposmic, eight were adequately hyposmic, and one was mildly hyposmic. In Group 2, five patients were moderately hyposmic, five were mildly hyposmic, and two cases were normosmic. In Group 3, two individuals were mildly hyposmic, and the remaining 11 were normosmic. Average ± standard deviation of OBV values was 60.08±5.35 mm^3 and 71.29±6.55 mm^3 in Group 1 and Group 2, respectively. These values differed significantly between the two groups (p<0.005).

Total CCCRC score was 4±0.7 in Group 1 (moderately hyposmic), 5.08±0.70 in Group 2 (mildly hyposmic), and 6.42±0.31 in Group 3 (normosmic). The differences in CCCRC scores among the groups were statistically significant (p=0.001) (Table 2).

When healthy individuals (Group 3) were compared with other groups, the OB volumes of them were significantly higher than those of the pre-treatment group (p<0.005), but comparable with the values in the post-treatment group (p=0.24). However, CCCRC scores of healthy individuals were significantly higher than those in both pre-treatment and post-treatment groups.

DISCUSSION

HBO therapy is a medical technique in which high pressure pure oxygen is provided to the patient in a special cabin or a custom-made system consisting of several chambers. Undersea and Hyperbaric Medical Society states that 100% pure oxygen should be applied at a pressure of at least 1.4 atm (11).

For physiological effects to occur, HBO therapy should elevate plasma oxygen level to 0.3-6 ml/L under 3 ATA pressure. HBO

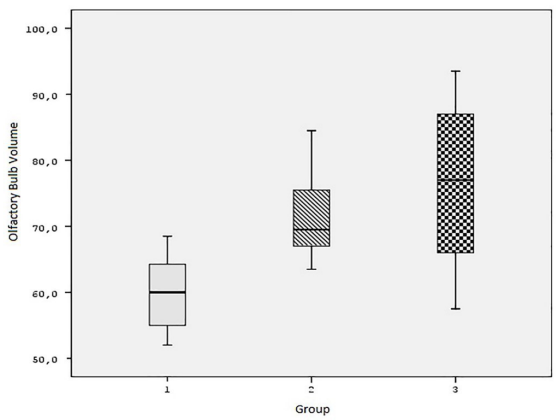

Figure 3: Boxplots for OBV of the groups of pre-treatment patients, post-treatment patients, and healthy individuals.

Table 2: Descriptive statistics of all groups

	Group 1-Pre-treatment n=12			Group 2- Post-treatment n=12			Group 3-Healthy n=13		
Variables	**Mean**	**SD**	**Range**	**Mean**	**SD**	**Range**	**Mean**	**SD**	**Range**
Age (yr)	54.2	3.2	50-60	54.2	3.2	50-60	55.2	4.2	50-63
CCCRC	4	0.7	2.5-4.5	5.1	0.7	4-6	6.4	0.3	5.75-7
OBV	60.1	5.4	54.5-68.5	71.3	6.6	63.5-84.5	76.5	11.4	57.5-93.5

CCCRC: Connecticut Chemosensory Clinical Research Center test score, OBV: Olfactory Bulb Volume

therapy provides many physiological, medical, and physical effects into action. It maximizes tissue oxygenation by increasing the oxygenated hemoglobin in solution and oxygen content (12). The American Diabetes Association approves HBO therapy as an adjuvant option in diabetic neuropathies that are unresponsive to any other treatment, are inoperable, and are life-threatening, especially when associated with ischemia (13).

A different study has proven that the hypobaric environment causes lower scores in the olfactory thresholds compared to the hyperbaric environment (14).

A group of 40 healthy volunteers were evaluated olfactory functions under hyperbaric 2.4 (atm abs) and 1 absolute atmosphere (atm abs) environment. Olfactory functions were shown to increase significantly with hyperbaric conditions (15).

Olfaction tests have been utilised as preclinical indicators to prognosticate the development and onset of various diseases with inflammatory processes (16).

Sequalae related to macrovascular diseases such as ischemia are assumed to be adversely affected. Additionally with the coexistence of DM and olfactory dysfunction, it has been reported that olfactory function scores are less in terms of DM-related complications (17).

Olfactory dysfunction in diabetic patients may be due to olfactory nerve damage, which is a sign of central neuropathy. It has been shown that the ability of patients to identify odors correctly decreases with increasing intensity of peripheral neuropathy. Olfactory dysfunction may occur in DM patients due to conduction or sensorineural problems (18,19).

The mechanisms causing the possible development and progression of olfactory dysfunction in patients with DM are unknown. Many hypotheses have been tried to explain the underlying mechanisms, including direct effects on the olfactory nerve or the central nervous system due to micro- and macrovascular changes or other abnormalities (20).

Olfactory dysfunction may happen in DM patients due to a weakened olfactory nerve. Therefore, it is an indicator of central neuropathy. Compatible with the former articles, all diagnostic scores were significantly lower in the diabetic olfactopathy group in this study, suggesting that the olfactory nerve is affected by DM similarly to that of the other cranial nerves. Further studies on these existing findings are needed to define whether olfactory testing and OBV measurement can be regarded as a test for diagnosis of central diabetic neuropathy.

In our study, it has been shown that OBV was remarkebly smaller in patients with type-2 diabetic olfactopathy compared to the healthy individuals with the same age group. An improvement in olfactory tests and an increase in OBV after HBO treatment was observed in patients with DM, which could be an indicator of a potential improvement in neuropathic progression.

This is a preliminary study. This type of research is very costly, and the number of cases has been tried to be limited and kept to a minimum. For this reason, studies have been conducted with cases close to the number of cases taken in previous MRI studies on olfactory bulb.

The reason for taking hyperbaric oxygen therapy was not diabetic olfactopathy, the patients were randomly selected from patients who underwent HBO treatment protocol for diabetic foot. Therefore, the HBO treatment duration, dose and treatment scheme is the standard diabetic foot protocol and has not been changed.

Smell function disorders in diabetes are a highly controversial issue. While planning this study, it was designed according to the study of Veyseller et al. In the literature and in their study, they reported an improvement in odor functions with HBO treatment in diabetic patients. In our study, we obtained results that support their study findings in relation to patients with diabetic olfactopathy in olfactory functions. However, in our study, we conducted a preliminary study to see whether HBO therapy has an effect on olfactory bulb. This study aims to shed light on future treatments and studies.

OB has a plastic structure. In people who have been away from olfactory stimuli for years, Veyseller et al. reported an increase in OB volumes after treatment in laryngectomy patients and showed that even after years, OB increased in volume with its plastic structure. Therefore, we have shown in this study that there is an increase in OB volumes in diabetic patients, even if the mechanism is not fully known.

CONCLUSION

In this study, a significant olfactory dysfunction was observed in patients with T2-DM compared to healthy individuals. This is a preliminary study to report that OBV is decreased in patients with diabetic olfactopathy and that OBV can improve with HBO therapy.

Ethics approval was obtained from the Istinye University, Research Ethics Committee before the study (Date: 07.10.2020, no: 2/2020.K-067). All patients in this study signed a written informed consent form for participation. This work was done in accordance with the principles of the Declaration of Helsinki.

Ethics Committee Approval: This study was approved by Istinye University Clinical Research Ethics Committee (Date: 07.10.2020, No: 2/2020.K-067).

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RESEARCH ARTICLE
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Evaluation of the Relationship Between Mandibular Condyle and Related Arterial Structures by Computed Tomographic Angiography

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ABSTRACT

Objective: Iatrogenic injuries of internal maxillary artery (IMA) and external carotid artery (ECA) during temporomandibular and retromandibular region surgeries are serious surgical complications with high mortality and morbidity. In order to avoid this complication, it is important for surgeons to know these vascular structures' course and their relationship with the mandibular condyle and ramus. The aim of this study was to reveal the relationship of the IMA and ECA with the mandible by head and neck computed tomography (CT) angiography.
Materials and methods: Bilateral head and neck CT angiography data in 26 patients (52 region) were evaluated retrospectively. The spatial distance of IMA and ECA to the mandible was calculated in all three planes (IMAx, ECAx, IMAy, ECAy, IMAz, ECAz planes). The presence of vascular tortuosity and contact were also evaluated.
Results: We have found that the nearest distance to the ramus of the ECA before giving a branch to IMA was 32.5±7.7 mm above the line drawn tangent to the lower border of corpus mandible. The internal maxillary artery was measured to be in contact with the medial cortical surface of the mandibular condyle in 39 of the 52 angiographies. This contact point was found to be 1.74 mm in front of the posterior margin of the ramus.
Conclusion: In this study, we radiologically confirmed that the internal maxillary artery is in close association with the mandibular condyle. It is important for surgeons to be aware of this neighborhood in order to prevent intraoperative vascular injuries.

Keywords: Internal maxillary artery, external carotid artery, temporomandibular joint surgery, computed tomography angiography

INTRODUCTION

Even though major bleeding is not very common in temporomandibular joint surgery (TMJ), it is a serious complication that can be life-threatening when it occurs. Along with the external ear and facial nerve, the superficial temporal artery and internal maxillary artery are among the structures that can be injured during TMJ surgery (1). Sidebottom et al. stated that intraoperative bleeding during a total joint replacement operation was an uncommon but serious condition in only two of the one hundred cases which they included in their study (2). In these two cases, the bleeding was due to hemorrhage from a maxillary artery which was trapped inside the ankylotic tissue (2). Major intraoperative hemorrhages require the surgeon to immediately deal with this situation, which can sometimes require the external carotid artery (ECA) to be ligated or involve vessels being selectively embolized (3).

The internal maxillary artery (IMA), an important vascular structure that can be injured during TMJ and ramus surgery, leaves the ECA behind the ramus of the mandible before

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entering the infratemporal fossa (4). The aim of this study was to evaluate the relationship of the internal maxillary artery and its originating point from the ECA with the mandibular condyle and ramus on Computed Tomography Angiography (CTA) images.

MATERIAL AND METHOD

This study was approved by the ethics committee of Istanbul University, Istanbul Faculty of Medicine (Date: 02.10.2022, no: 24). Written consent was obtained from all the patients regarding the usage of their CTA images. We measured data from the CTA images of 26 patients, aged 21 to 82, who were referred to the Istanbul Faculty of Medicine Department of Neuroradiology. The data were collected retrospectively from patients who were suspected for vascular diseases of the neck. Imaging was performed on a Toshiba 64 Aquilion computed tomography (CT) scanner (Toshiba Medical Systems, Nasu, Japan) with injecting contrast material at the arterial stage. The reformatted images were evaluated retrospectively on a Toshiba CT workstation. To put a mark on axial CTA images for measuring the distance between the point where the internal maxillary artery (IMA) gets closest to the medial aspect of the mandibular condyle and the lower margin of the mandible, on coronal and sagittal reformatted images, the position of the maxillary artery in relation to the mandibular condyle was measured. We used the center tool on CTA images for marking the reference point (Figure 1).

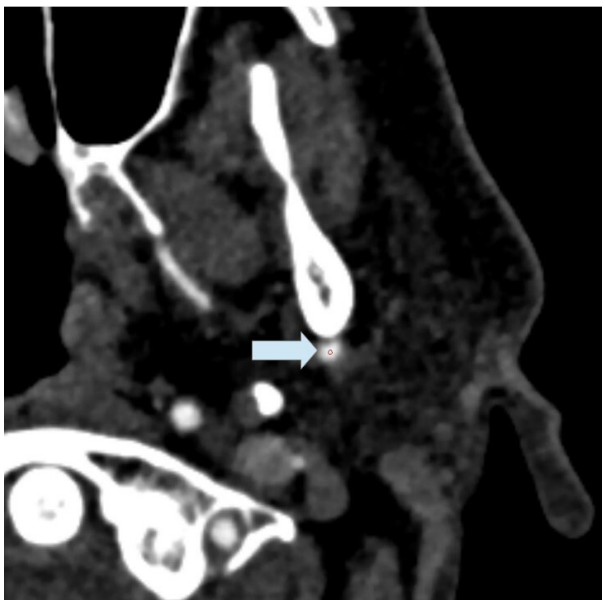

Figure 1: In the axial computed tomography angiograph image, the arrow shows the small red circle which marks the artery's nearest point to the surface of the condyle (in contact with the posterior surface of the mandibular condyle).

ECAx: The distance between the originating point of the IMA where it departs from the ECA and the imaginary line drawn tangent to the lower margin of the mandibular body (Figure 2-A).

IMAx: The distance between the point where the IMA gets closest to the medial aspect of the mandibular condyle and the lower margin of the mandible. If IMA was located posterior to the posterior margin of the condyle, this measurement was recorded as the distance between IMA and the imaginary line drawn tangent to the lower margin of the mandibular body (Figure 2-A).

ECAy: The distance between the originating point of the IMA where it departs from the ECA and the posterior margin of the condyle. When this originating point was found to be posterior to the posterior margin of the condyle, the measurement was recorded as minus (-) (Figure 2-B).

IMAy: The distance between the point where the IMA gets closest to the medial aspect of the mandibular condyle and the posterior margin of the condyle (Figure 2-C).

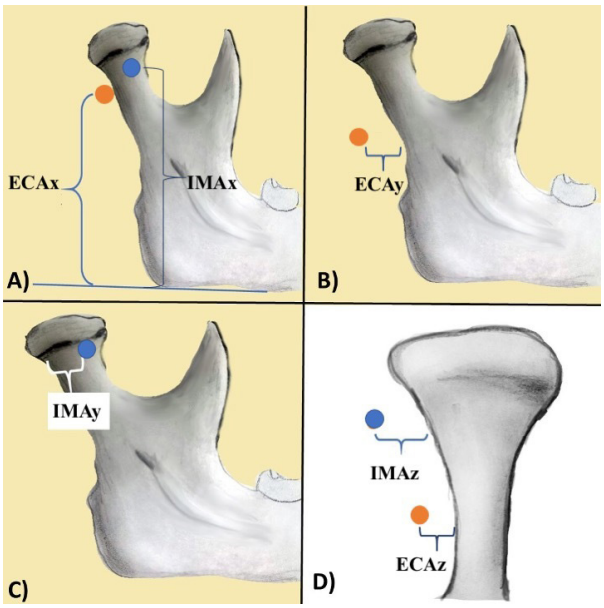

Figure 2: In the sagittal (A, B, C) and coronal (D) planes illustrations, the orange points mark the originating point of the internal maxillary artery (IMA) where it departs from the ECA and the blue points mark the point where the IMA gets closest to the medial aspect of the mandibular condyle. A) ECAx (the distance between the orange point and the imaginary line drawn tangent to the lower margin of mandibular body) and IMAx (the distance between the blue point and the lower margin of the mandible) measurements. B) ECAy (the distance between the orange point and the posterior margin of the condyle. When this originating point was found to be posterior to the posterior margin of the condyle, the measurement was recorded as minus (-)) measurement. C) IMAy (the distance between the blue point and the posterior margin of the condyle) measurement. D) IMAz (the distance between the blue point and the medial aspect of the mandibular condyle) and ECAz (the distance between the orange point and medial aspect of the mandibular condyle. When the ECAy was a minus value, ECAz was not measured) measurements.

ECAz: The distance between the originating point of the IMA where it departs from the ECA and medial aspect of the mandibular condyle. When the ECAy was a minus value, ECAz was not measured (Figure 2-D).

IMAz: The distance between the point where the IMA gets closest to the medial aspect of the mandibular condyle and the medial aspect of the mandibular condyle (Figure 2-D).

Statistical Analysis

Descriptive statistical analyses were performed for all the variables examined in this study. Compliance with the normal distribution of the data obtained by measurement was established using the Kolmogorov Smirnov and Shapiro-Wilk tests. The data obtained by measurement were expressed as mean ± standard deviation and median (min-max).

The relationships between the measurement levels were given by calculating the Spearman correlation coefficient. Statistical significance was accepted as p<0.05 and two-tail.

RESULTS

Evaluation of the measurements have shown a statistically significant positive relationship at medium strength between the measurements ECAx and IMAx (rs=0.584; p<0.001) (Table 1), (Figure 3). A low negative correlation between ECAy and IMAy measurements was found to be statistically significant (rs=0.301; p=0.03).

Between the measurements IMAx and IMAy there was a statistically significant, moderately positive relation (rs=0.706; p<0.001), and between IMAy and IMAz, there was a weak negative relation which was statistically significant. (rs=-0.444; p=0.002) (Figure 4).

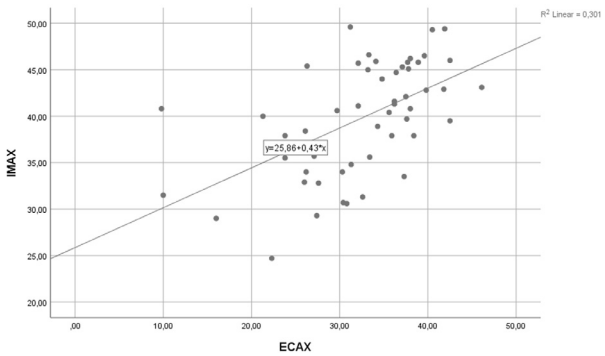

Figure 3: Relation between ECAx and IMAx

ECAx: The distance between the originating point of the IMA where it departs from the ECA and the imaginary line drawn tangent to the lower margin of mandibular body.
IMAx: The distance between the point where the IMA gets closest to the medial aspect of the mandibular condyle and the lower margin of the mandible. If IMA was located posterior to the posterior margin of the condyle, this measurement was recorded as the distance between IMA and the imaginary line drawn tangent to the lower margin of the mandibular body.

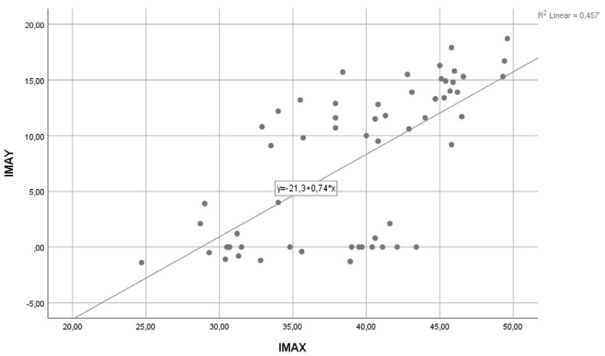

Figure 4: Relation between IMAx and IMAy

IMAx: The distance between the point where the IMA gets closest to the medial aspect of the mandibular condyle and the lower margin of the mandible. If IMA was located posterior to the posterior margin of the condyle, this measurement was recorded as the distance between IMA and the imaginary line drawn tangent to the lower margin of the mandibular body.
IMAy: The distance between the point where the IMA gets closest to the medial aspect of the mandibular condyle and the posterior margin of the condyle.

Table 1: Distribution of measurements of the joints included in the study

	ECAx	ECAy	ECAz	IMAx	IMAy	IMAz
Mean	32.51	-1.08	3.20	39.22	7.74	0.35
Std. Deviation	7.71	2.58	2.96	6.19	6.78	0.65
Median	**33.75**	**-1.55**	**3.65**	**40.40**	**10.00**	**0.00**
Minimum	9.80	-5.30	0.00	24.70	-1.40	0.00
Maximum	46.1	10.1	7.9	49.6	18.7	2.8

(ECA: external carotid artery, IMA: internal maxillary artery) ECAx: The distance between the originating point of the IMA where it departs from the ECA and the imaginary line drawn tangent to the lower margin of mandibular body. ECAy: The distance between the originating point of the IMA where it departs from the ECA and the posterior margin of the condyle. When this originating point was found to be posterior to the posterior margin of the condyle, the measurement was recorded as minus (-). ECAz: The distance between the originating point of the IMA where it departs from the ECA and medial aspect of the mandibular condyle. When the ECAy was a minus value, ECAz was not measured. IMAx: The distance between the point where the IMA gets closest to the medial aspect of the mandibular condyle and the lower margin of the mandible. If IMA was located posterior to the posterior margin of the condyle this measurement was recorded as the distance between IMA and the imaginary line drawn tangent to the lower margin of the mandibular body. IMAy: The distance between the point where the IMA gets closest to the medial aspect of the mandibular condyle and the posterior margin of the condyle. IMAz: The distance between the point where the IMA gets closest to the medial aspect of the mandibular condyle and the medial aspect of the mandibular condyle.

The relationship between IMAz and IMAx was also weakly negative and statistically significant (rs=-0.397; p=0.002). Two of the patients with bilateral tortuosity had the IMAz measurement as 0 twice on both sides, which meant that the artery had contact with the bone at two points on each side. Tortuosity was observed in four patients, three of whom had bilateral tortuosity of the maxillary artery. All of the patients with tortuosity of the maxillary artery had a distance of 0 mm in measurement z plane.

We have found that the nearest distance of the ECA before giving a branch to IMA was 32.5±7.7 mm above the line drawn tangent to the lower border of the corpus mandible. The IMA was measured to be in contact with the medial cortical surface of the mandibular condyle in 39 of the 52 angiographies. This contact point was 1.74 mm anterior to the posterior margin of the ramus. The nearest distance to the posterior margin was measured to be 0 mm (the artery makes contact with the bone on the posterior margin of the mandibular condyle), and the highest distance of the contact was measured to be 18.7 mm anterior to the posterior margin of the mandibular condyle. The average distance of this point from the lower border of the mandible was 39.7 mm. The lowest contact point between the IMA and bone was at 28.7 mm, the highest was at 49.6 mm.

DISCUSSION

The internal maxillary artery (IMA) departs from the ECA behind the ascending ramus of the mandible before entering the infratemporal fossa. It continues anteriorly, leaving the pterygopalatine fossa and the pterygomaxillary fissure behind to divide into two branches in the infratemporal fossa as the IMA enters the fossa lateral to the lateral pterygoid muscle, which consists of two parts (upper and lower) inserting into the temporomandibular joint (TMJ) (4). Surgeries involving the TMJ and mandibular condyle are prone to hemorrhages resulting from the injury of the IMA. The anatomy of the maxillary artery, which is an important route of blood supply to the soft and hard tissues of the maxillofacial region, has been an interest of research both radiographically and macroscopically (5-10).

Researchers have reported a great variety of anatomical courses for the maxillary artery and the originating point has been studied by several researchers (5). Authors have used various measurement landmarks for the origin of the maxillary artery since there is not a consensus on how to measure this anatomical structure. Takarada and Ikakura et al. used the mandibular ramus, whereas Ito et al. measured its distance to the eye-ear plane corresponding to the superficial temporal artery (11-13). Ikakura and Takarada et al. reported the origin of the maxillary artery to be as high as 2/5 to the posterior border of the mandibular ramus in most of the subjects (80%). In the present study, we have found that the nearest distance of the ECA before giving a branch to IMA was 32.5±7.7 mm above the line drawn tangent to the lower border of the body of the mandible (11, 12).

The positive relation between the values ECAx and IMAx is not surprising since it shows that the higher the maxillary artery departs from the external carotid, the higher it lies anteriorly. When we evaluate the positive relation between ECAx and IMAx, we observe that when the maxillary artery departs from the external carotid at a higher level, this may mean that it approaches the medial aspect of the condyle at a more anterior point. However, it must be kept in mind that the results of the present study show that this positive relation is weak.

Also, the positive relation between the measurements IMAx and IMAy point to a course of the maxillary artery in which the more cranially the maxillary artery is located, the more anteriorly it approaches the medial aspect of the condyle. Our findings also show that, as the maxillary artery is located the closest to the medial aspect of the condyle, there is a possibility that this point is more anterior to the posterior margin of the condyle and more cranial to the lower margin of the mandibular ramus (negative relation between IMAy and IMAz, and negative relation between IMAx and IMAz respectively).

Otake et al. have reported that the maxillary artery runs lateral to the external pterygoid muscle in 94.6% of their specimens (5). Even though we have not evaluated the relationship between the pterygoid muscle and the maxillary artery, our findings state that the maxillary artery can be very close to the medial aspect of the mandibular condyle. The maxillary artery was measured to be in contact with the medial cortical surface of the mandibular condyle in 39 of the 52 angiographies. However, there was no statistically significant relationship between this contact and measurements in other planes.

Our findings have shown that of the 39 angiographs in which the IMA was measured to be in contact with the medial aspect of the mandibular condyle, this contact point was 1.74 mm anterior to the posterior margin of the ramus. The nearest distance to the posterior margin was measured to be 0 mm (the artery makes contact with the bone on the posterior margin of the mandibular condyle), and the highest distance of contact was measured to be 18.7 mm anterior to the posterior margin of the mandibular condyle. These findings suggest that during any surgical procedures involving the mandibular condyle, the surgeon must be aware that the MA may be in contact with the condyle between the most posterior margin and 18.7 anterior to the posterior margin.

The average distance of this point from the lower border of the mandible was 39.7 mm. The lowest contact point between the MA and bone was at 28.7 mm and the highest was at 49.6 mm, which also must be considered by the surgeon.

Tortuosity can be observed on the course of the maxillary artery, which can make interventions to this anatomical structure difficult in infratemporal fossa surgery (14). It has been previously stated that detection of the tortuosity of the maxillary artery was crucial for the procedures for controlling epistaxis (15). We have found tortuosity in 15.38% of the patients and this was bilateral in 11 of the patients.

A drawback of the present study is the preference of anatomical points related to the mandible, which is a mobile bone, and

these measurements may change according to the mandibular position. Several authors have chosen various anatomical structures as landmarks for anatomical studies in the past. Talebzadeh et al. selected stable measurement points, such as the outer aspect of the zygomatic arc and the line drawn from the uppermost point of the glenoid fossa (16). Otake et al. measured the distance between the originating point of the maxillary artery and the external auditory canal (5).

The anatomical landmarks used in the present study were selected due to their direct involvement in the temporomandibular joint surgery. Structures such as the lower border of the mandible and the mandibular condyle are visible to the surgeon in various surgical approaches, such as the preauricular approach or submandibular approach. The weaknesses of this study are the small number of patients included in the study and the fact that it was performed retrospectively on CT angiography of patients who were examined for vascular diseases.

CONCLUSION

The present study confirms that the internal maxillary artery is in close relationship with the mandibular condyle and ramus. Therefore, the risk of internal maxillary artery injury should be considered in light of this close relationship in surgical procedures involving the mandibular condyle.

Ethics Committee Approval: This study was approved by Istanbul Faculty of Medicine Clinical Research Ethics Committee (Date: 02.10.2022, no: 24).

Informed Consent: Written informed consent was obtained.

Peer Review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study- M.B., Y.E., N.S.S., B.A.; Data Acquisition- M.B., Y.E., B.A., A.Ö., H.İ., N.S.S.; Data Analysis/Interpretation- H.İ., M.B., Y.E., B.A.; Drafting Manuscript- Y.E., M.B., A.Ö., H.İ., B.A.; Critical Revision of Manuscript- Y.E., H.İ., M.B., N.S.S., B.A.; Final Approval and Accountability- M.B., Y.E., B.A., N.S.S.; Material or Technical Support- A.O., H.İ.; Supervision- B.A., N.S.S., Y.E.

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RESEARCH ARTICLE
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Predictive Value of Fine Needle Aspiration Biopsy and Ultrasonography in The Diagnosis of Cervical Lymphadenopathy*

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ABSTRACT

Objective: Cervical lymphadenopathy (LAP) is one of the most common pathologies in adults and children. While ultrasonography (USG) and fine needle aspiration biopsy (FNAB) are the two methods used as diagnostic tests, excisional biopsy is the gold standard method for diagnosis. In this study, we aimed to show the relationship between USG findings and FNAB results with malignancy in patients with LAP.
Materials and methods: Patients who visited our clinic with the complaint of cervical LAP between March 2020 and September 2022 and underwent excisional biopsy were included in this retrospective study. The number, distribution, side, size, cortical thickness, conglomeration, and necrosis characteristics of LAP were evaluated on USG. The sensitivity and specificity of the FNAB were calculated in patients in accordance with the histopathological results.
Results: Of the patients included in the study, 45 were female and 42 were male. The overall mean age was 32.72 ± 20.02. The sensitivity of the FNAB was 43.5% and the specificity was 90.0%. Advanced age, presence of conglomeration, unilateral LAP, and generalized LAP were found to be statistically significant in terms of malignancy, while cortical thickness, the number and size of LAPs, and necrosis were not statistically significant.
Conclusion: FNAB was not found to be a reliable test to rule out malignancy due to low sensitivity for determining malignancy and but was found to be a highly selective test, and the malignancy-suspected result detected the real patients quite successfully. The advanced age, unilateral LAP, generalized distribution, and conglomeration were the parameters supporting malignancy.

Keywords: Cervical lymphadenopathy; excisional biopsy; fine needle aspiration biopsy; ultrasonography

INTRODUCTION

Lymphadenopathy (LAP) is defined as abnormal changes in a lymph node's size and/or character because of the migration of inflammatory or neoplastic cells to the lymph nodes (1, 2). Cervical LAPs arise from various causes, mainly infectious and neoplastic processes, and they need to be assessed with a detailed and multidisciplinary approach. Patients presenting with cervical LAP should be examined comprehensively in terms of features such as patient's age, onset and duration of LAP, changes in size and growth rate, pain, presence of B symptoms, and presence of accompanying systemic findings that may support malignancy (dyspnea, dysphagia, otalgia, etc.). If necessary, advanced laboratory tests, imaging methods (USG, Computed Tomography, Magnetic Resonance Imaging), and biopsy (fine needle aspiration biopsy, core needle biopsy, excisional biopsy) are performed (3).

While inflammatory pathologies are more frequent in children and young adults, neoplastic causes are more common with

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increasing age (2, 3). USG is a cheap, rapidly accessible, and non-invasive method in the evaluation of cervical LAP in terms of malignancy (4). In USG, parameters such as the number, distribution, size, shape, cortex, hilus of lymph nodes, and presence of necrosis are evaluated. An increase in the number of LAPs, generalized distribution, irregular borders, thick cortex, non-echogenic hilum, and necrosis are among the USG findings that can be interpreted in favor of malignancy (4-7).

Fine needle aspiration biopsy (FNAB) in suspicious lymph nodes is one of the minimally invasive methods that can be used in the diagnosis. Although FNAB is not a diagnostic method alone in the diagnosis of hematological malignancies, the diagnostic success rate of FNAB varies between 75-98% (8, 9). Non-diagnostic samples, high false-negative rates in Hodgkin lymphoma, and incomplete classification in Non-Hodgkin lymphoma are among the disadvantages of FNAB (8-10).

In this study, we aimed to present the role of FNAB and USG in diagnosis in patients with cervical LAP with the literature by comparing the preoperative USG features and FNAB reports with postoperative histopathological results of patients admitted to our clinic with a complaint of LAP.

MATERIALS AND METHODS

A total of 87 patients who underwent lymph node excision between March 2020 and September 2022 at the Otorhinolaryngology Clinic of Atatürk University Medical Faculty Hospital were included in this retrospective study. The study was carried out with the approval of Atatürk University Faculty of Medicine Clinical Research Ethics Committee dated September 29, 2022, numbered 590. Informed consent was obtained from the patients. Patients with a known diagnosis of a disease that can cause LAP (hematological malignancy, epithelial tumor history, thyroid cancer history, etc.) were excluded from the study.

The systemic examinations in terms of lymphadenopathy and neck ultrasonography reports of all patients participating in the study were investigated by scanning the medical files. In USG results, the number, distribution, side, size (long axis of LAP), cortical thickness, conglomeration, and necrosis characteristics of LAP were recorded. Patients were divided into groups according to the number of LAPs (single or multiple), distribution of LAP (localized: having only cervical LAP and generalized: inguinal and/or axillary LAP in addition to cervical LAP), side of the LAP (unilateral and bilateral), and size of LAP (between 1.5 and 2 cm, between 2 and 3 cm, and greater than or equal to 3 cm).

The histopathological results of patients who underwent FNAB before excisional biopsy were categorized as malignant and reactive. The concordance and differences between the FNAB and excisional biopsy histopathological results of the patients were investigated.

SPSS 20.0 (SPSS Inc., Chicago, IL, USA) program was used for data analysis. In the statistical analysis of the study, mean ± standard deviation was used for continuous variables, whereas frequency and percentage values were defined for categorical variables. General characteristics and demographic features of the groups were determined by Frequency (Descriptive analysis: frequency analysis for a single variable) analysis. Since the findings in the data did not follow normal distribution according to the Kolmogorov-Smirnov (K-S) test, nonparametric tests were applied. In pairwise comparisons, the Mann-Whitney U Test was used to compare the mean of two independent groups. The Kruskal-Wallis Test was applied for the mean comparison of multiple independent groups. Post-Hoc Tamhane's T2 analysis was used for multiple comparisons. Chi-square test was used to define the relationship between categorical variables. A $p \leq 0.05$ value was considered statistically significant throughout the entire study.

RESULTS

Patients aged between 2 and 80 (32.72±20.02) were included in the study. 45 (51.7%) of the patients were female and 42 (48.3%) were male. FNAB was studied in 43 (49.4%) patients preoperatively. The histopathological results were reactive LAP in 31 (72.1%) of the patients who underwent FNAB, and the results were suspicious for malignancy in 12 (27.9%) of them. When the excisional biopsy pathology results of all patients were analyzed, the result was reactive in 48 (55.2%) patients, compatible with hematological malignancy in 29 (33.3%) patients, and compatible with other malignancies in 10 (11.5%) patients (Table 1).

FNAB and excisional biopsy results of 43 patients who previously underwent FNAB were compared. The positive predictive value of FNAB was 83.3% and the negative predictive value was 58.1%. The sensitivity value of FNAB was 43.5% and the specificity value was 90.0% (Table 2).

Table 1: Age, gender, FNAB, and excisional biopsy results of cervical LAP patients

			n=87
Age	**Mean ± SD (min-max)**		32.72±20.018 (2-80)
Gender	Female	n (%)	45 (51.7)
	Male	n (%)	42 (48.3)
FNAB	Absent	n (%)	44 (50.6)
	Present	n (%)	43 (49.4)
Result of FNAB	Absent	n (%)	44 (50.6)
	Reactive	n (%)	31 (35.6)
	Suspicious for malignancy	n (%)	12 (13.8)
Result of excisional biopsy	Reactive	n (%)	48 (55.2)
	Hematological malignancy	n (%)	29 (33.3)
	Other malignancies	n (%)	10 (11.5)

FNAB: Fine needle aspiration biopsy, SD: Standard deviation

Excisional biopsy results were divided into two groups as reactive and malignant. There were 48 (55.17%) patients in the reactive LAP group and 39 (44.83%) patients in the malignant LAP group. Reactive and malignant LAP groups were statistically analyzed based on age, gender, and USG features, and those data are presented in Table 3.

As summarized in Table 3, increased age (p=0.001), generalized LAP (p= 0.011), unilateral LAP (p=0.015), and LAP presenting with conglomeration (p=0.004) had statistically significant results in favor of malignancy throughout the comparison between reactive and malignant LAP groups. On the other hand, no statistically significant data was obtained from the comparison of groups by gender of patients (p=1.000), the number of LAPs (p=0.105), size of LAP (p=0.097) as well as displaying thick cortex (p=0.519) and necrosis (p=0.720).

Table 2: Comparison of FNAB and Excisional Biopsy Results

		Result of Excisional Biopsy			p
		Malignant	Reactive	Total	
Result of FNAB	Suspicious for Malignancy	10 (%83.3)	2 (%16.7)	***12***	***0.019****
	Reactive	13 (%41.9)	18 (%58.1)	31	
	Total	23	20	43	

FNAB: Fine needle aspiration biopsy

It was reported from the analysis that the risk of a malignancy-positive result was increased 3.15 times by a unilateral LAP, 4.88 times by generalized LAP, and 3.92 times by a LAP presenting with conglomeration.

DISCUSSION

Cervical LAP is a common pathology in both pediatric and adult populations. If the LAP grows rapidly within 2 weeks, if there is no reduction in LAP dimensions within 4-6 weeks, and if it does not disappear completely within 8-12 weeks, a biopsy should be performed (1). There are similarities and differences in cervical LAP characteristics between adult and pediatric patients. Generalized LAP and LAP in the supraclavicular region have an increased risk for malignancy in both children and adults, and biopsy should be considered without delay (2, 11). LAP size greater than 1.5 cm in the cervical region in adult patients raises suspicion for malignancy, while LAP greater than 2 cm in pediatric patients is more significant in terms of malignancy (2, 11).

While cervical LAP is more likely to be malignant in advanced age (>40), benign pathologies are more frequent in children and young adults (2, 3). In our study, the mean age of the patients was calculated as 32.72±20.02 (2-80). In the comparison between age and LAP between the reactive and malignant LAP groups, there was a statistically significant difference between advanced age and the possibility of LAP being malignant. The comparison for age was found to be compatible with the literature.

Table 3: Characteristics of Excisional Biopsy Results

			Reactive n=48	Malignant n=39	p	OR (Odds ratio)
Age	Mean ± SD		24.00±16.678	43.46±18.668	***0.001****	
Gender	Female	n (%)	25 (52.1)	20 (51.3)	1.000	
	Male	n (%)	23 (47.9)	19 (48.7)		
Increase in cortical thickness	Absent	n (%)	25 (52.1)	17 (43.6)	0.519	
	Present	n (%)	23 (47.9)	22 (56.4)		
Conglomeration	Absent	n (%)	37 (77.1)	18 (46.2)	***0.004****	***3.92***
	Present	n (%)	11 (22.9)	21 (53.8)		
Number of LAP	Multiple	n (%)	45 (93.8)	32 (82.1)	0.105	
	Single	n (%)	3 (6.2)	7 (17.9)		
Side of LAP	Unilateral	n (%)	12 (25.0)	20 (51.3)	***0.015****	***3.15***
	Bilateral	n (%)	36 (75.0)	19 (48.7)		
Size of LAP	1.5-2 Cm	n (%)	18 (37.5)	17 (43.6)	0.097	
	2-3 Cm	n (%)	21 (43.8)	9 (23.1)		
	≥3 Cm	n (%)	9 (18.8)	13 (33.3)		
Distribution of LAP	Localized	n (%)	44 (91.7)	27 (69.2)	***0.011****	***4.88***
	Generalized	n (%)	4 (8.3)	12 (30.8)		
Necrosis	Absent	n (%)	46 (95.8)	32 (82.1)	0.720	
	Present	n (%)	2 (4.2)	7 (17.9)		

LAP: Lymphadenopathy

In cervical LAPs, FNAB is an inexpensive, rapid diagnostic, and minimally invasive procedure compared to excisional biopsy. The most significant disadvantages of FNAB are the inability to subtype hematological malignancies, nondiagnostic sampling, and high false negative rates. Although FNAB is currently one of the most frequently used diagnostic methods in cervical masses, the gold standard method in the diagnosis of LAP is excisional biopsy (8).

In the literature, the sensitivity of FNAB in diagnosis varies between 62% and 100%. (12) In our study, the sensitivity was found to be 43.5% and the specificity was 90.0%. Our sensitivity value was found to be low when compared to the literature values, yet the specificity was coherent with the literature (8, 10, 12, 13). In our study, we also discovered that the positive predictive value of FNAB was 83.3% and the negative predictive value was 58.1%. When sensitivity and negative predictive value data were evaluated together, it was determined that FNAB was not a sensitive test for malignancy and was not reliable enough to rule out malignancy.

In our study, the specificity of FNAB in terms of malignancy was 90% and the positive predictive value was 83.3%. When the positive predictive value was evaluated together with the specificity, it was seen that FNAB is a highly selective test in our clinic and the suspicious for malignancy result indicated the real patients quite successfully.

The size, location, number, shape, cortex, echogenicity, and presence of necrosis of the LAP can be investigated by USG. Increased number of LAP, supraclavicular location of LAP, size greater than 2 cm in children and 1.5 cm in adults, the ratio of short to long axis (S:L) ≥0.5 cm, increased cortical thickness, absence of echogenic hilus, and presence of necrosis can be interpreted in favor of malignancy, although it is not specific (5, 6).

In the comparison between the reactive LAP group and the malignant LAP group in terms of the number of LAPs (single or multiple), no statistically significant difference was observed. In the comparison carried out in terms of LAP distribution (localized or generalized), the generalization of LAP was a statistically significant feature in terms of malignancy. It was observed that generalized LAP increased the probability of malignancy 4.88 times. In a study by Darnal et al., generalized LAP was found in 53% of 45 patients with primary malignancies (14). In the study of Kamat on 244 cases with generalized LAP, the most common cause was granulomatous disease (58.19%) followed by reactive LAP (30.73%), then hematological and other malignancies (11.04%) (15). The presence of generalized LAP in a patient does not necessarily signify that patient has a diagnosis of malignancy; however, they should be examined for granulomatous diseases and malignancies.

Side features (unilateral or bilateral) of malignant LAP have brought controversial results in studies. In a study by Çelenk et al. on the pediatric population, 31% of patients with benign pathology had unilateral LAP, and 69% had bilateral LAP; on the other hand, it was found that 30% of patients with malignant pathology had unilateral LAP and 70% had bilateral LAP (16). In another study conducted by Kartal et al. in patients younger than 20 years of age, the unilateral/bilateral ratio was 69.8%/30.2% in the benign group, and 93.2%/ 6.8% in the malignant group. It was determined that unilateral LAP gave significant results in terms of malignancy (17). In our study, 25% of the reactive LAP group had unilateral LAP and 75% had bilateral LAP; 51.3% of the malignant LAP group had unilateral LAP and 48.7% had bilateral LAP. We determined that unilateral LAP was a statistically significant characteristic in terms of malignancy and unilateral LAP increased the probability of malignancy 3.15 times.

In the study, LAPs were examined in 3 groups (between 1.5 to 2 cm, between 2 to 3 cm, and greater than or equal to 3 cm) according to their size, and in the analysis performed among the three groups, it was discovered that the size did not cause a significant difference in terms of malignancy. In the study by Kartal et al., LAP size was evaluated according to the short and long axis. In the malignant group, the mean of the short axis was 18.7±8.8 mm and in the benign group, the mean of the short axis was 13.7±7.3 mm; hence, there was a statistically significant difference between the malignant-benign groups (17). In our study, it can be assumed that a statistically significant difference could not be obtained since the short and long-axis values were not calculated separately when measuring the LAP size.

The increase in thickness of the LAP cortex is one of the features that arouse the suspicion of a pathological LAP. In a study by Kurt et al. on cervical LAP, the hilar:cortical thickness ratio was examined, and cortical thickness gave a statistically significant result in favor of malignancy (18). In this study, groups were separated according to the presence of an increase in cortical thickness, and no statistically significant difference was obtained between the reactive LAP group and the malignant LAP group.

Contradictory results have been concluded from the literature about the relationship between lymph node conglomeration and malignancy. In a study by Khanna et al. with 192 patients, it was determined that conglomeration did not create a statistically significant difference between malignant and benign lesions, while in the study by Kartal et al., conglomeration was detected as a significant variable between benign and malignant groups (17, 19). In our study, the conglomeration of LAP was determined to be statistically significant in terms of malignancy and it was observed that conglomeration increased the probability of malignancy by 3.92 times.

The presence of necrosis in LAP is another feature that supports malignancy. In our study, 4.2% of the reactive LAP group and 17.9% of the malignant LAP group had LAP with necrosis. Despite the fact that there were more patients with necrotic LAPs in the malignant LAP group, no statistically significant difference was defined between the groups. In the study conducted by Kartal et al., necrosis was observed in 4.7% of the reactive group and 18.2% of the malignant group, and a

statistically significant difference was found between the two groups. (17) In another study conducted by Vandana et al., necrosis was seen at a rate of 30% in patients with tuberculosis, and at a rate of 5% in patients with a malignant diagnosis, while necrosis was observed at a rate of 7.5% in the reactive group (4). Considering all these data, it is concluded that necrosis supports malignancy and granulomatous diseases such as tuberculosis.

There are several limitations of this study. First, the pediatric and adult patients were evaluated together. Examining these two populations separately would give more objective results. Secondly, carrying out such a study with larger patient groups will give more comprehensive and accurate results. Finally, not examining the lymph nodes with elastography is another limitation of this study.

CONCLUSION

Although cervical lymphadenopathy is mostly caused by benign pathologies, it is a pathology that should be investigated extensively in terms of malignancy, particularly in elderly patients. As a result of our study, it was observed that the specificity and positive predictive values of FNAB were quite high. However, its sensitivity and negative predictive values were lower. When we focus on the USG features, unilateral LAP, generalized distribution, and presence of conglomeration provide significant information for indicating malignancy. We believe that conducting studies with larger patient groups about this topic will provide more consequential results to the literature.

Ethics Committee Approval: This study was approved by Ataturk University Faculty of Medicine Clinical Research Ethics Committee (Date: 29.09.2022, No: 590).

Informed Consent: Written informed consent was obtained.

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CASE REPORT
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Acute Mediastinitis Caused by Parapharyngeal Abscess and Carotid Sheath Infection: Case Report

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ABSTRACT

Deep neck infections are less common today than in the past. Still, odontogenic infections due to tooth decay and periodontal disease are common in the community. Although odontogenic infections in general are locally limited, they can progress to deep neck infections and lead to life-threatening complications in exceptional cases. Mediastinal extensions of deep neck infections are a condition that requires rapid diagnosis and should be considered first in patients who have a worsening general condition and swelling in the face - neck extending to the bottom of the clavicle and who have a toxic appearance. These infections need immediate treatment. A rapid and accurate clinical, radiological and multidisciplinary approach toward our case was demonstrated to be lifesaving.

Keywords: Abscess, deep neck infection, mediastinitis, odontogenic

INTRODUCTION

Deep neck infection (DNI) is one of the most important emergencies in otolaryngology practice. DNI, which may cause life-threatening complications such as mediastinitis, Lemierre syndrome, necrotizing cervical fasciitis, carotid artery aneurysm, and sepsis, is a clinical picture that requires prompt diagnosis and treatment (1,2).

In this case report, we present a parapharyngeal abscess case caused by an odontogenic infection complicated by acute descending necrotizing mediastinitis.

CASE REPORT

A fifty-three-year-old female patient was admitted to our clinic with complaints of toothache, sore throat, inability to eat, and swelling in the right cheek that started a few days before. She had diabetes mellitus in her background.

The physical examination of the patient revealed tooth decay in the right third molar. There was swelling on the right parotid and submandibular gland, which was palpable with pain but did not fluctuate (Figure 1a). The laboratory values of the patient were as follows: leukocytes 16160/ml, neutrophils 13950/ml, and C-reactive protein 329.4 mg/l. With the preliminary diagnosis of deep neck infection, ceftriaxone 2x1 g i.v. infusion and metronidazole 2x500 mg i.v. infusion treatment were started empirically with intravenous hydration and analgesia.

Upon the extension of swelling on the right side of the patient's neck below the clavicle and the worsening of her general condition, emergency contrast-enhanced neck and thorax tomography were performed. In these radiological examinations, the right parapharyngeal abscess and subsequent acute descending necrotizing mediastinitis were observed, the thoracic surgery unit was informed, and the patient was taken to emergency surgery (Figure 2a). Following the right-sided Schobinger incision, the submandibular gland was turned over the anterior and the intense abscess was drained from the parotid deep lobe region and posterior of the submandibular gland extending to the parapharyngeal area. Upon the appearance of intense purulent secretion in

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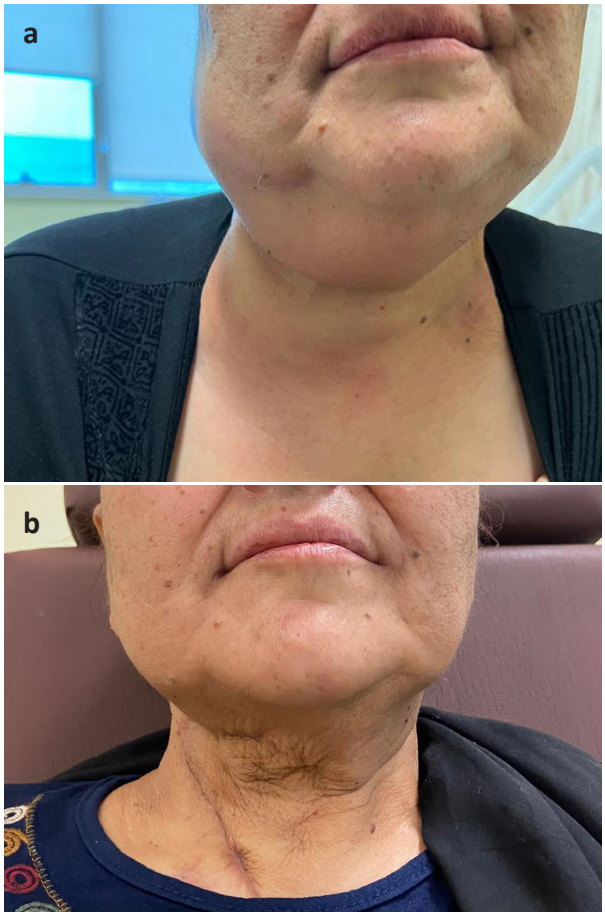

Figure 1: a) Swelling due to deep neck infection from the right side of the patient's face and neck to the bottom of the clavicle and b) Image of the healed patient.

the localization of the carotid sheath, the sheath was opened from the skull base to the level of the clavicle. The inside of the sheath was also found to be filled with intense purulent secretion (Figure 3a). Following this, the clavicular region was explored and the necrotic tissues were cleaned. The layers were closed appropriately and the patient was transferred to thoracic surgery in the same session. After double lumen intubation, the thoracoscopic entrance was performed through video-assisted thoracic surgery (VATS). The exploration showed infiltration of abscess content from the mediastinum into the thorax. About 600 cc of empyema content was aspirated. It was revealed that the mediastinal surface was necrotized starting from the level of the azygos to the level of the apex. Upon opening the mediastinum with the help of a harmonic scalpel, it was observed that the inflammation came from the edges of the esophagus, trachea, and vena cava superior (VCS). The inflammatory content was aspirated and necrotic tissues were also debrided (Figure 3b). After intrapleural lavage, a thoracic tube was inserted, the expansion of the lung was observed, and the layers were duly closed.

The patient was followed in the intensive care unit (ICU) for approximately 15 days, one week of which was with intubation, and in the otolaryngology clinic for about three weeks. Upon

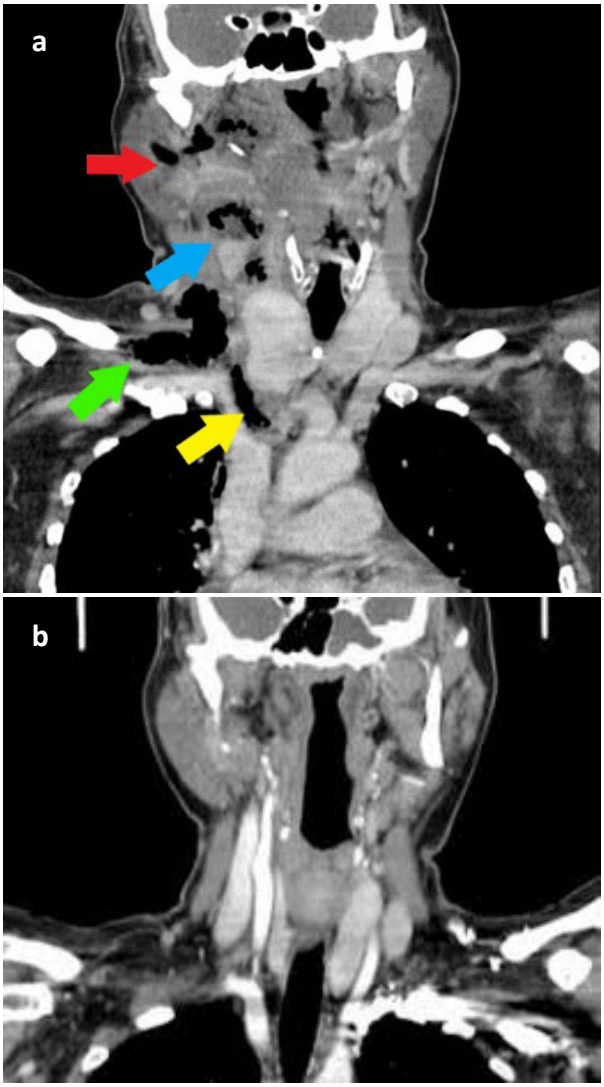

Figure 2: Contrast-enhanced coronal neck CT imaging shows a) a deep neck abscess with air bubbles, starting from the parotid cavity (red arrow), extending to the parapharyngeal and visceral space inferiorly (blue arrow), which opened to the danger space and spread to the mediastinum (yellow arrow); the swelling starting under the clavicle in the physical examination (green arrow). b) In the coronal plane tomography image of the patient three months later, the abscess areas in the neck and mediastinum were completely healed and had a natural appearance.

restoring the oral intake and turning radiological images and laboratory parameters to normal, the patient was discharged with recommendations (Figure 2b**)**. No pathology was detected in the follow-up examinations of the patient for six months (Figure 1b).

DISCUSSION

Deep neck infections most often originate from the septic foci of the mandibular teeth, tonsils, parotid gland, deep cervical lymph nodes, middle ear, or sinuses (3). Although a rare complication, the mediastinal spread of deep neck infections

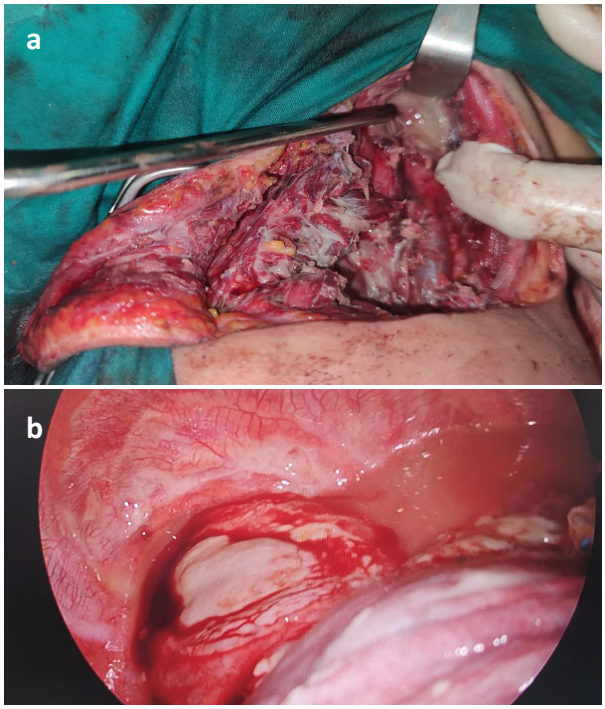

Figure 3: a) Dense purulent secretion in the right carotid sheath and b) rapidly developing pleural empyema and the appearance which is consistent with acute inflammation and mediastinitis in the right upper mediastinal pleura.

is an important complication to consider in a toxic-looking patient. Early diagnosis of mediastinitis is difficult due to the uncertainty of its symptoms. The initial findings are mostly retrosternal pain due to cervical infection, swelling in the cheek-neck, stiffness, crepitation, and trismus, and they may progress to sepsis in a short time following the detection of infection.

The main steps of treatment are the selection of antibiotics appropriate to the etiological agent and surgical drainage (4). The mortality rate is high in cases that cannot be diagnosed early or treated correctly/adequately. The surgical intervention type is determined by the extent of infection in the mediastinum. For drainage of the visceral compartments in the mediastinum, video-assisted thoracic surgery (VATS) or thoracotomy may be needed. When deciding on drainage in cases with infection foci such as parapharyngeal and retropharyngeal ones, it is crucial to detect whether local suppuration has occurred, or whether the infection is in the cellulite stage. Imaging methods can be used because it is sometimes difficult to decide on abscess formation by clinical examination. Surgical drainage of the neck and mediastinum is necessary for deep neck infections complicated by acute necrotizing mediastinitis. The mediastinal approach is performed by the cervicomediastinal or transthoracic method. Although the cervical approach can be effective in early mediastinitis, thoracotomy is usually indicated when the necrotizing process enters the “danger space” (5, 6). In our case, since an abscess involving all the parapharyngeal region and the carotid sheath developed, we planned to clean all abscess foci by achieving full control of the surgical area in the neck with a Schobinger incision. Following the drainage of the abscess region to the level of the clavicle, the patient was transferred to the thoracic surgery unit.

Another important issue in deep neck infections is providing airway control. Therefore, when necessary, intubation and even tracheotomy can be performed (3). In our case, insufficient oral opening due to trismus prevented endotracheal intubation. Therefore, we performed nasotracheal intubation.

In our case, the rapid extension of the swelling from the lower level of the neck to the bottom of the clavicle and the rapid deterioration of the general condition of the patient made us think that acute mediastinitis was developing, and requested emergency contrast tomography. Thus, we detected mediastinal spread with parapharyngeal and carotid sheath abscesses in the patient. Our case has demonstrated that in situations where deep neck infection progresses and becomes complicated, the rapid application of a multidisciplinary approach is lifesaving.

Informed Consent: Written informed consent was obtained.

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Author Contributions: Conception/Design of Study- İ.E., B.A.; Data Acquisition- İ.E., B.A.; Data Analysis/Interpretation- İ.E., B.A.; Drafting Manuscript- İ.O., İ.E., B.A., S.Y.; Critical Revision of Manuscript- S.Y., İ.E., B.A., İ.O.; Final Approval and Accountability- İ.O.; Material or Technical Support- S.Y., B.A., İ.O.; Supervision- S.Y., İ.E.

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CASE REPORT
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A Rare Cause of Facial Nerve Paralysis: Hemangioma Located in the Tympanic Portion of the Facial Nerve

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ABSTRACT

Facial nerve hemangiomas are rare tumors and benign lesions. These tumors may involve all segments of the facial nerve. The most common location of these tumors are geniculate fossa of the facial nerve. The tympanic portion of the facial nerve is rarely involved. To our knowledge, two cases are reported in the literature. These tumors may cause symptoms due to the compression of adjacent structures, such as facial nerve paralysis and hearing loss. Computed tomography imaging and magnetic resonance imaging are useful tools for diagnosis and viewing the extent of the tumor. Surgical excision is the primary treatment for these tumors. In this study, we report the third case of facial nerve hemangioma located in the tympanic portion of the facial nerve in the literature. The tumor was located in the tympanic segment and presented with total facial nerve paralysis.

Keywords: Facial nerve, hemangioma, tumor

INTRODUCTION

Facial nerve (FN) tumors are uncommon tumors. Facial nerve hemangiomas (FNH) are rare entities and benign lesions. These tumors have a slow growth pattern and account for 18% of all facial nerve tumors (1). FNH may involve all segments of the facial nerve. Pulec reported the first case of hemangioma involving geniculate ganglion of the facial nerve (2). FNH stem from the venous plexus around the FN and not from the FN itself. The term 'hemangioma' is commonly accepted to describe these tumors, but there are clinical findings suggesting that they are vascular malformations and not vascular tumors. The most common location of the FNH is the geniculate fossa. Other location sites are internal auditory canal (IAC) and the second genu of the facial nerve (1). They may cause symptoms due to the compression of adjacent structures, such as facial nerve paralysis and hearing loss. First line treatment for these tumors is surgical excision, and the type and extent of surgery is related to tumor location, tumor site, and preoperative hearing level (2).

In this study, we report the third case of FNH in the literature. The tumor was located in the tympanic segment and presented with total facial nerve paralysis.

CASE REPORT

A 61-year-old patient presented to the Zonguldak Bulent Ecevit University Department of Otolaryngology clinic with progressive left facial weakness during the previous six-month history and a one-month history of left total facial paralysis (House-Brackmann grading score VI). Steroid therapy had been given previously, and the patient was referred to our clinic for further investigation due to progressive facial nerve paralysis despite steroid therapy. He had no hearing changes, tinnitus, or vertigo. An otoscopy showed intact and normal tympanic membranes. Audiometry revealed normal hearing. A physical examination revealed total left facial paralysis with no muscle movement.

Computed tomography (CT) showed a round-shaped soft-tissue density lesion in the middle ear, close to the mastoid portion of

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the FN (Figure 1). With magnetic resonance imaging (MRI), an expansive lesion with irregular contours, involving the tympanic segment of the left facial nerve and posteriorly, in its transition to the mastoid segment, was noted. Slight enhancement of contrast agent was suggestive of facial nerve schwannoma (Figure 2). Facial electromyography revealed severe total axonal degeneration findings in the facial nerve. Surgery was planned for the patient. Posterior tympanotomy with the left retroauricular transmastoid approach was performed. The tumor was located in the tympanic portion extending between the geniculate ganglion and the second genu of the FN. The incus was removed to provide more exposure. Once the tumor was reached, it is noted that the tumor was interspersed with the FN; therefore, it was impossible to dissect the tumor from the FN. To provide complete tumor excision, we decided to perform the segmental excision of the FN including the lesion, as well as end-to-end interposition grafting with the left greater auricular nerve. The lesion was excised with the facial nerve tympanic segment and second genu. Then, the greater auricular nerve graft material was placed between the two ends of the tympanic portion of the facial nerve, and fibrine glue was applied to stabilize the grafting material in place. The incus was replaced between the malleus and stapes and stabilized with bone cement. Lastly, left lateral tarsorrhaphy was performed in order to minimize orbital complaints. For histologic examination, hematoxylin-eosin staining was performed, and it revealed vascular structures with a single layer endothelium on surface with loose connective tissue (Figure 3). The diagnosis was made as FNH. There was no change in the facial function of the patient, and no tumor recurrence was observed during the six-months follow-up period.

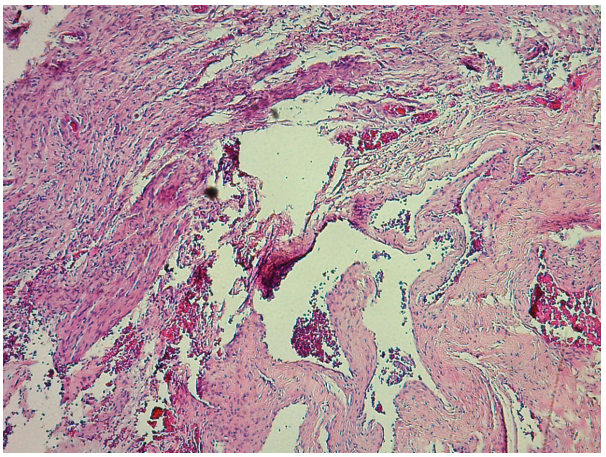

Figure 3: Hematoxylin-eosin staining revealed multiple vascular structures with a single layer endothelium on surface with loose connective tissue.

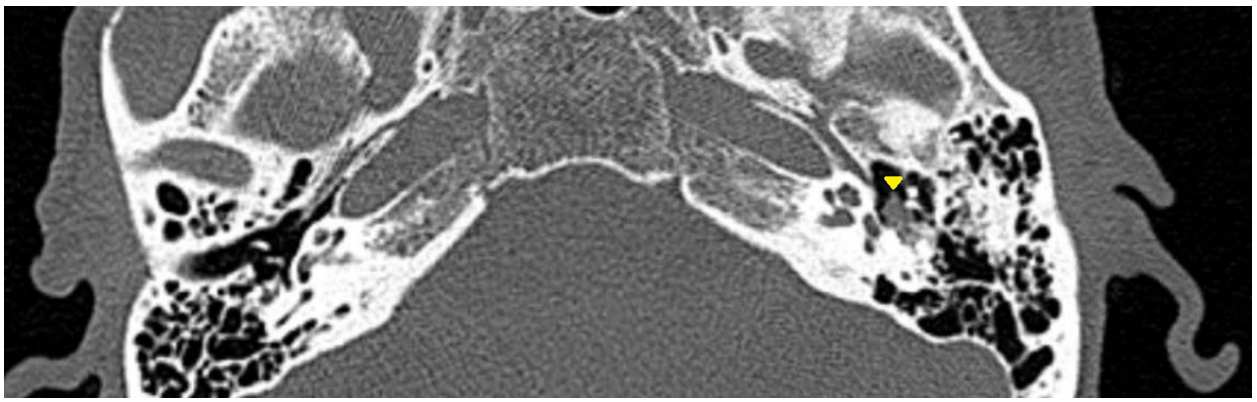

Figure 1: CT of the patient with hemangioma of the tympanic segment. Note the soft tissue attenuated mass centered in the tympanic segment of the facial canal.

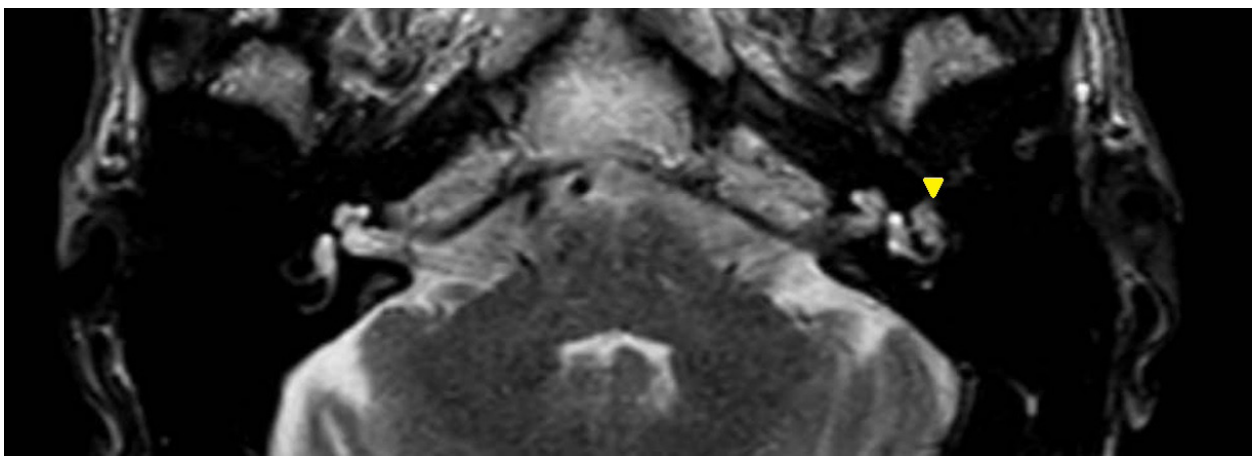

Figure 2: Axial T2-weighted image demonstrating an ill-defined mass lesion in the left tympanic cavity.

DISCUSSION

FNH are benign lesions but their underlying pathogenesis is unclear. They most commonly involve the geniculate ganglion of the FN (3). Also, the underlying mechanism for the reason of hemangioma preference for the geniculate ganglion is not completely understood. Balkany et al. suggested in their study that the presence of high perineural capillary density in the geniculate portion of the FN in comparison with its other segments may be the reason for tendency of FNH (3). In our knowledge, four cases of FNH involving the mastoid segment of the FN are reported in the literature. Hopkins et al., Piccirillo et al and Eby et al. reported a total of four patients with facial nerve hemangiomas involving the mastoid segment of the facial nerve (4-6). The hemangiomas involved in the tympanic portion of the facial nerve are relatively uncommon, with only a few cases having been reported in the literature. Friedman et al. reported in their study that two cases of hemangioma involved geniculate ganglion and tympanic portions of the FN (7). Saliba and Fayad reported in their study a facial nerve hemangioma case located in the second genu of the FN (8). Santos et al. reported the second case in the literature of FNH involving the tympanic portion of the FN. To our knowledge, this is the third FNH located in the tympanic portion of the FN in the literature (9).

Facial nerve hemangiomas may compress or invade adjacent structures and may cause severe symptoms (10). Some possible symptoms in patients with facial nerve hemangioma are recurrent or persistent unilateral facial paralysis, tinnitus, and ear fullness. Occasionally, hemangioma involves the IAC and unilateral sensorineural hearing loss or vertigo may also occur (11). The clinical presentation of patients with tympanic portion facial nerve hemangiomas has not yet been well described because this condition is rare (11). In our case, the patient had left grade 6 facial nerve paralysis, and an audiometry test revealed normal hearing.

Diagnosis of the FNH is based on imaging. In a CT scan, hemangioma may contain calcified intra-tumoral spicules resembling honeycomb may be noticed. A tumor may also cause the irregular expansion of the surrounding bone. Hemangiomas are hypointense on Tl-weighted MRI and hyperintense on T2-weighted images, and they show contrast enhancement with gadolinium (11,12) . Differentiation of the other facial nerve tumors in the same region, such as schwannomas, tend to have a similar appearance in imaging. Although considered pathognomonic, the honeycomb appearance of facial nerve hemangiomas in a CT scan is present in approximately 50% of cases, and unfortunately, this pattern may not be reliable (13). In the absence of this finding, differential diagnosis from schwannomas or other rarer facial nerve neoplasms, such as meningioma, may be difficult (14).

The first line treatment for FNH is surgical excision, but FNH in the tympanic segment of the FN are very rare vascular tumors, and therefore there is no consensus on their management (2). Propranolol, surgical excision, and close follow ups are possible treatment options for hemangiomas in the tympanic portion of the FN. For patients with normal facial function, close follow ups without excision may be appropriate (15). The type and extent of surgical approach depends on tumor location, tumor size, and preoperative hearing level. Since the tumor is extraneural, it is possible to remove it while preserving the FN in some cases. However, in some cases, it is not possible to preserve the FN because of direct nerve infiltration.

Small hemangiomas result in less compression of the nerve, making it possible to surgically remove the tumor while preserving nerve function (16). Large hemangiomas are usually interspersed with the FN, therefore it is difficult to excise the tumor from the nerve, and it is often necessary to remove the involved portion of the facial nerve and repair it with end-to-end primary anastomosis or interposition with a graft. In our case, we performed FN partial excision and repaired it using end-to-end interposition grafting with greater auricular nerve. We used fibrine glue to stabilize the grafting material in place. There are some conflicting reports on the management of these injuries, with the timing of surgery being one of the most controversial subjects. The recurrence of FNH is rare after complete or partial excision (17).

CONCLUSION

Facial nerve hemangiomas should be considered as a possible cause of facial paralysis in the differential diagnosis of middle ear tumors.

Informed Consent: Written informed consent was obtained.

Peer Review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study- D.B., M.D.; Data Acquisition- M.D.; Data Analysis/Interpretation- D.B., M.D.; Drafting Manuscript- D.B.; Critical Revision of Manuscript- D.B.; Final Approval and Accountability- D.B.; Material or Technical Support- F.K., B.A.; Supervision- D.B.

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CASE REPORT
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Maxillomandibular Cysts and Multiple Basal Cell Carcinomas Due to Gorlin-Goltz Syndrome: A Case Report

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ABSTRACT

Maxillomandibular cysts may be encountered frequently and they may be the first signs of various syndromes. In Gorlin-Goltz syndrome, skeletal, ocular and dermal lesions may accompany the maxillomandibular cysts. In order to reach a diagnosis, a thorough evaluation and a multidisciplinary approach are required. In this study, a patient with multiple maxillomandibular cysts and multiple basal cell carcinomas was presented.

Keywords: Basal cell carcinoma; Gorlin-Goltz syndrome; maxillomandibular cyst; odontogenic keratocyst

INTRODUCTION

Gorlin-Goltz syndrome is a rare autosomal dominant genetic disorder which involves dermal and skeletal anomalies (1). This syndrome is also referred as nevoid basal cell carcinoma syndrome (NBCCS) (1). It is mostly characterized by basal cell carcinomas (BCC), odontogenic keratocysts (OKC), palmar and plantar pitting, facial dysmorphism and opthalmologic and skeletal abnormalities (1). Diagnosis of the patients is based on clinical, radiological and histopathological findings.

NBCCS has a prevalence of 1 in every 56,000 to 256,000 individuals (2). A classical triad is described by Robert James Gorlin and Robert William Goltz, which consists of multiple basal cell carcinomas, jaw cysts and skeletal abnormalities (2). In addition, many other clinical manifestations are present in NBCCS. In order to reach a diagnosis, major and minor diagnostic criteria should be fulfilled (3). Due to the complexity of clinical manifestations, a multidisciplinary approach is necessary for diagnosis and follow-up (4).

CASE PRESENTATION

In January 2022, a 19 year-old female patient was referred to a dental clinic with mandibular swelling. Due to the presence of multiple maxillomandibular cysts at the panoramic graph, the patient was consulted to the Plastic Reconstructive and Aesthetic Surgery Department (Figure 1). The patient did not report any relevant personal or familial history.

In physical examination, mandibular swelling was seen by both intraoral and extraoral examination. In fact, both hemimandibles and left hemimaxilla were affected. Poor dental hygiene was seen during the intraoral examination, and bilateral lower gingivobuccal sulci and left hemimaxilla were expanded. These swollen areas were solid and expansile and

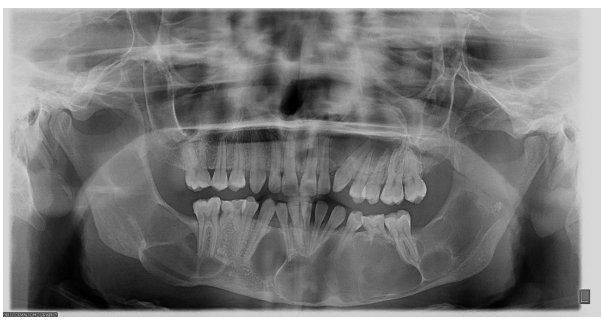

Figure 1: Preoperative panoramic radiograph of the patient is demonstrated.

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there was not any pulsation over the lesions. A computerized tomography was performed in order to confirm the localization of the cysts (Figure 2).

After further evaluation, excisional biopsy was performed under general anesthesia. During the routine follow-up of the patient, multiple pigmented lesions were detected on various parts of the body such as face and trunk. The dermal and maxillomandibular lesions were regarded as classical manifestations of NBCCS and the patient was referred to the Dermatology department. The patient underwent total body confocal dermoscopy and suspicious lesions of the back, the left preauricular area, the right malar region and the right lumbar region were biopsied with a punch device.

Histopathological findings of the maxillomandibular cysts confirmed the diagnosis of odontogenic keratocyst and all punch biopsy specimens were reported as basal cell carcinoma (Figure 3,4). The skin lesions were resected with a healthy tissue margin of 5 millimeters and no local recurrence was seen during the follow-up period of two years. The patient was referred for further genetic tests; however, she refused the consultation.

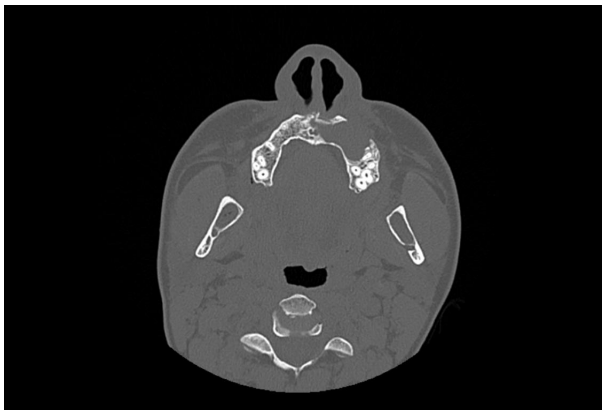

Figure 2: Preoperative computed tomography demonstrates the cystic lesion on the left side of the maxilla.

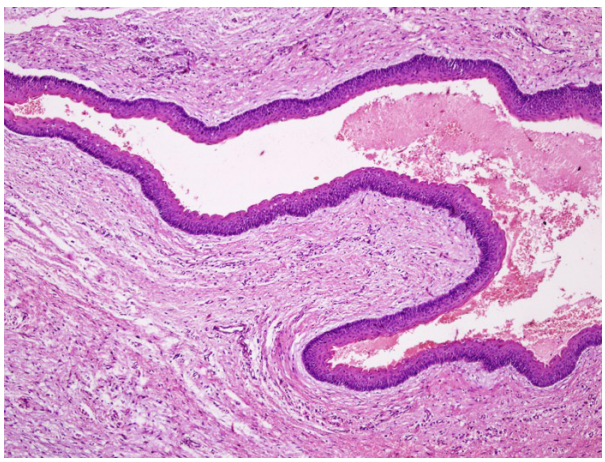

Figure 3: Histopathological appearance of the maxillary lesion showing characteristic lining of odontogenic keratocyst (OKC).

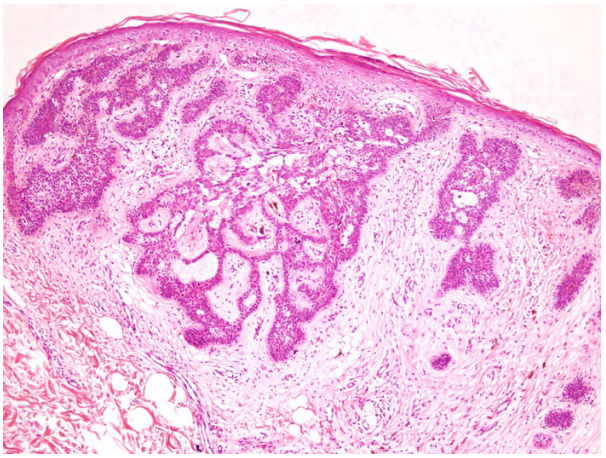

Figure 4: Histopathologic appearance of the basal cell carcinoma lesion on back of the patient.

Major criteria	Minor criteria
1. More than 2 BCCs or one under the age of 20 years 2. Odontogenic keratocysts of the jaw proven by histology 3. Three or more palmar or plantar pits 4. Bilamellar calicification of the falx cerebri 5. Bifid, fused or markedly splayed ribs 6. First degree relative of NBCC syndrome	1. Macrocephaly determined after adjustment of height 2. Congenital malformations: cleft lip or palate, frontal bossing, moderate or severe hypertelorism 3. Other skeletal abnormalities: Sprengel deformity, marked pectus deformity, marked syndactyly of the digits 4. Radiological abnormalities: Bridging of the sella turcica, vertebral anomalies, hand and foot deformities 5. Ovarian fibroma 6. Medulloblastoma

Figure 5: The diagnostic criteria of nevoid basal cell carcinoma syndrome are listed.

Biannual Plastic Reconstructive and Aesthetic Surgery and Dermatology follow-up visits were scheduled for the patient for both radiologic and dermoscopic surveillance.

DISCUSSION

Nevoid basal cell carcinoma syndrome is an uncommon autosomal dominantly inherited disorder with a mutation in the PTCH1 gene (1). Maxillomandibular cysts may be an initial sign of the syndrome (1). Patients with this syndrome may develop BCCs during childhood; however, the median age of onset is 20 years (3). In this case, the development of maxillomandibular cysts and the early onset of the dermal lesions supported the diagnosis.

In NBCCS, palmar pits occur in 75% to 90% of patients and medulloblastoma is the second most common malignancy (4).

In addition, skeletal anomalies are frequent and falx cerebri calcification, bifid ribs, frontal bossing, cleft lip/palate and vertebral fusions may be seen (3, 4). Such pathologies were not present in this case.

The diagnosis requires a multidisciplinary approach due to the variety of clinical manifestations. NBCCS may be established when two major or one major and two minor criteria are present (4). These criteria are listed in Figure 5. In this case, the patient had three major criteria including jaw cysts, multiple BCCs, palmar pitting and a minor criteria such as frontal bossing.

CONCLUSION

In NBCCS, early diagnosis enables the reduction of the complications, the prevention of the progression of the less frequent manifestations and the detection of the hereditary risk of the patient's family. Physicians should be aware of the variety of the clinical features of NBCCS.

Informed Consent: Written informed consent was obtained.

Peer Review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study- E.G., E.K., A.A.; Data Acquisition- E.G., E.K., A.A.; Data Analysis/Interpretation- E.G.; Drafting Manuscript- E.G., A.A.; Critical Revision of Manuscript- E.K.; Final Approval and Accountability- E.G., E.K., A.A.; Material or Technical Support- E.G.; Supervision- E.K.

Conflict of Interest: The authors have no conflict of interest to declare.

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The editor informs the reviewers that the manuscripts are confidential information and that this is a privileged interaction. The reviewers and editorial board cannot discuss the manuscripts with other persons. The anonymity of the referees must be ensured. In particular situations, the editor may share the review of one reviewer with other reviewers to clarify a particular point.

PEER REVIEW

Peer Review Policies
Only those manuscripts approved by its every individual author and that were not published before in or sent to another journal, are accepted for evaluation.

Submitted manuscripts that pass preliminary control are scanned for plagiarism using iThenticate software. After plagiarism check, the eligible ones are evaluated by editor-in-chief for their originality, methodology, the importance of the subject covered and compliance with the journal scope.

The editor hands over the papers matching the formal rules to at least two national/international referees for double-blind peer review evaluation and gives green light for publication upon modification by the authors in accordance with the referees' claims.

Responsibility for the Editor and Reviewers
Editor-in-Chief evaluates manuscripts for their scientific content without regard to ethnic origin, gender, citizenship, religious belief or political philosophy of the authors. Editor-in-Chief provides a fair double-blind peer review of the submitted articles for publication and ensures that all the information related to submitted manuscripts is kept as confidential before publishing.

Editor-in-Chief is responsible for the contents and overall quality of the publication. He/She must publish errata pages or make corrections when needed.

Editor-in-Chief does not allow any conflicts of interest between the authors, editors and reviewers. Only he has the full authority to assign a reviewer and is responsible for final decision for publication of the manuscripts in the Journal.

Reviewers must have no conflict of interest with respect to the research, the authors and/or the research funders. Their judgments must be objective.

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- Does the manuscript contain new and significant information?
- Does the abstract clearly and accurately describe the content of the manuscript?
- Is the problem significant and concisely stated?
- Are the methods described comprehensively?
- Are the interpretations and consclusions justified by the results?
- Is adequate references made to other Works in the field?
- Is the language acceptable?

Reviewers must ensure that all the information related to submitted manuscripts is kept as confidential and must report to the editor if they are aware of copyright infringement and plagiarism on the author's side.

A reviewer who feels unqualified to review the topic of a manuscript or knows that its prompt review will be impossible should notify the editor and excuse himself from the review process.

The editor informs the reviewers that the manuscripts are confidential information and that this is a privileged interaction. The reviewers and editorial board cannot discuss the manuscripts with other persons. The anonymity of the referees is important.

Manuscript Organization and Submission

The manuscripts should be prepared in accordance with ICMJE-Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (updated in December 2015 - http://www.icmje.org/icmje-recommendations.pdf). Author(s) are required to prepare manuscripts in accordance with the CONSORT guidelines for randomized research studies, STROBE guidelines for observational original research studies, STARD guidelines for studies on diagnostic accuracy, PRISMA guidelines for systematic reviews and meta-analysis, ARRIVE guidelines for experimental animal studies, and TREND guidelines for non-randomized public behavior.

Manuscripts can only be submitted through the journal's online manuscript submission and evaluation system, available at https://dergipark.org.tr/tr/journal/3565/submission/step/manuscript/new Manuscripts submitted via any other medium will not be evaluated.

Manuscripts submitted to the journal will first go through a technical evaluation process where the editorial office staff will ensure that the manuscript has been prepared and submitted in accordance with the journal's guidelines. Submissions that do not conform to the journal's guidelines will be returned to the submitting author with technical correction requests.

Author(s) are required to submit the following documents together with the manuscript and must ensure that the abstract and keywords are in line with the standards explained in below.

- **Copyright Agreement Form**
- **Author Form and ICMJE Potential Conflict of Interest Disclosure Form**
- **Ethics Committee Approval**
- **Cover Letter to the Editor**
- **Title Page**: A separate title page should be submitted with all submissions and this page should include:

- The full title of the manuscript as well as a short title (running head) of no more than 50 characters,
- Name(s), affiliations, academic degree(s) and ORCID ID(s) of the author(s),
- Grant information and detailed information on the other sources of support,
- Name, address, telephone (including the mobile phone number) and fax numbers, and email address of the corresponding author,
- Acknowledgment of the individuals who contributed to the preparation of the manuscript but who do not fulfil the authorship criteria.

Abstract: Abstract should be submitted with all submissions except for Letters to the Editor. The abstract of Original Articles should be structured with subheadings (Objective, Materials and Methods, Results, and Conclusion). Abstracts of Case Reports and Reviews should be unstructured. Abstracts should be 200-250 words.

Keywords: Each submission must be accompanied by a minimum of 3 to a maximum of 6 keywords for subject indexing at the end of the abstract. The keywords should be listed in full without abbreviations. The keywords should be selected from the National Library of Medicine, Medical Subject Headings database (http://www.nlm.nih.gov/mesh/MBrowser.html) .

Manuscript Types

Original Articles: This is the most important type of article since it provides new information based on original research. The main text of original articles should be structured with Introduction, Material and Method, Results, Discussion, and Conclusion subheadings..

Statistical analysis to support conclusions is usually necessary. Statistical analyses must be conducted in accordance with international statistical reporting standards (Altman DG, Gore SM, Gardner MJ, Pocock SJ. Statistical guidelines for contributors to medical journals. Br Med J 1983: 7; 1489-93). Information on statistical analyses should be provided with a separate subheading under the Materials and Methods section and the statistical software that was used during the process must be specified.

Units should be prepared in accordance with the International System of Units (SI).

Invited Review Articles: Reviews prepared by authors who have extensive knowledge on a particular field and whose scientific background has been translated into a high volume of publications with a high citation potential are welcomed. These authors may even be invited by the journal. Reviews should describe, discuss, and evaluate the current level of knowledge of a topic in clinical practice and should guide future studies. The main text should contain Introduction, Clinical and Research Consequences, and Conclusion sections. Please check Table 1 for the limitations for Review Articles.

Case Reports: There is limited space for case reports in the journal and reports on rare cases or conditions that constitute challenges in diagnosis and treatment, those offering new therapies or revealing knowledge not included in the literature, and interesting and educative case reports are accepted for publication. The text should include Introduction, Case Presentation, Discussion, and Conclusion subheadings. Please check Table 1 for the limitations for Case Reports.

Letters to the Editor: This type of manuscript discusses important parts, overlooked aspects, or lacking parts of a previously published article. Articles on subjects within the scope of the journal that might attract the readers' attention, particularly educative cases, may also be submitted in the form of a "Letter to the Editor." Readers can also present their comments on the published manuscripts in the form of a "Letter to the Editor." Abstract, Keywords, and Tables, Figures, Images, and other media should not be included. The text should be unstructured. The manuscript that is being commented on must be properly cited within this manuscript.

Tables

Tables should be included in the main document, presented after the reference list, and they should be numbered consecutively in the order they are referred to within the main text. A descriptive title must be placed above the tables. Abbreviations used in the tables should be defined below the tables by footnotes (even if they are defined within the main text). Tables should be created using the "insert table" command of the word processing software and they should be arranged clearly to provide easy reading. Data presented in the tables should not be a repetition of the data presented within the main text but should be supporting the main text.

Figures and Figure Legends

Figures, graphics, and photographs should be submitted as separate files (in TIFF or JPEG format) through the submission system. The files should not be embedded in a Word document or the main document. When there are figure subunits, the subunits should not be merged to form a single image. Each subunit should be submitted separately through the submission system. Images should not be labeled (a, b, c, etc.) to indicate figure subunits. Thick and thin arrows, arrowheads, stars, asterisks, and similar marks can be used on the images to support figure legends. Like the rest of the submission, the figures too should be blind. Any information within the images that may indicate an individual or institution should be blinded. The minimum resolution of each submitted figure should be 300 DPI. To prevent delays in the evaluation process, all submitted figures should be clear in resolution and large in size (minimum dimensions: 100 × 100 mm). Figure legends should be listed at the end of the main document.

All acronyms and abbreviations used in the manuscript should be defined at first use, both in the abstract and in the main text. The abbreviation should be provided in parentheses following the definition.

When a drug, product, hardware, or software program is mentioned within the main text, product information, including the name of the product, the producer of the product, and city and the country of the company (including the state if in USA), should be provided in parentheses in the following format: "Discovery St PET/CT scanner (General Electric, Milwaukee, WI, USA)"

All references, tables, and figures should be referred to within the main text, and they should be numbered consecutively in the order they are referred to within the main text.

Limitations, drawbacks, and the shortcomings of original articles should be mentioned in the Discussion section before the conclusion paragraph.

Revisions

When submitting a revised version of a paper, the author must submit a detailed "Response to the reviewers" that states point by point how each issue raised by the reviewers has been covered and where it can be found (each reviewer's comment, followed by the author's reply and line numbers where the changes have been made) as well as an annotated copy of the main document. Revised manuscripts must be submitted within 30 days from the date of the decision letter. If the revised version of the manuscript is not submitted within the allocated time, the revision option may be canceled. If the submitting author(s) believe that additional time is required, they should request this extension before the initial 30-day period is over. Accepted manuscripts are copy-edited for grammar, punctuation, and format. Once the publication process of a manuscript is completed, it is published online on the journal's webpage as an ahead-of-print publication before it is included in its scheduled issue. A PDF proof of the accepted manuscript is sent to the corresponding author and their publication approval is requested within two days of their receipt of the proof. The latest status of the submitted manuscripts and other information about the journal can be accessed at http://tr-ent.com. The editorial and publication processes of the journal are conducted in accordance with the guidelines of the International Council of Medical Journal Editors (ICMJE), the World Association of Medical Editors (WAME), the Council of Science Editors (CSE), the Committee on Publication Ethics (COPE), the European Association of Science Editors (EASE), and National Information Standards Organization (NISO). The journal conforms to the Principles of Transparency and Best Practice in Scholarly Publishing (doaj.org/bestpractice). An ORCID ID is required for all authors during the submission of the manuscript. The ID is available at http://orcid.org with free of charge.

Reference Style and Examples

Authors are responsible for supply complete and correct references. References should be numbered according to the order used in the text. Numbers should be given in brackets and placed at the end of the sentence. Examples are given below on the use of references. Reference end note style Vancouver

Periodicals: Author(s) Last Name initial(s) name of author(s) (if there are six or fewer authors, all authors should be written; if the number of authors are seven or more, only the first six of the authors should be written and the rest as "et al"). The title of the article, the abbreviated name of the journal according to the Index Medicus, Year; Volume (Issue): The first and last page numbers.

Example: Robson A, Greene J, Ansari N, Kim B. Eccrine porocarcinoma (malignant eccrine poroma): a clinicopathologic study of 69 cases. The American Journal of Surgical Pathology 2001;25:710-20. Books: Surname of the author(s) initial name(s) of author(s). The name of the book. The edition number. Place of publication: Publisher, Publication year.

Book chapters: The author (s) surname of the chapter initial (s) letter of the name. Section title. In: Surname of editor (s) initial (s) letter of first name (s) ed / eds. The name of the book. Edition number. Place of publication: Publisher, year of publication: The first and last page numbers of the chapter. Web address: If a "web" address is used as the reference address, the web address date should be given in brackets with the address. The DOI (Digital Object Identifier) number must be provided, when a web access article used in the text as a reference.

Example: AB Author, CD Author. Title of document. Retrieved from http://Web address (Accession date: aa/bb/2016).

Congress papers:

Thesis: Maden KL. Experimental investigation of the ..... Master Thesis, Health Science Institute of Ankara University, Ankara, 2005.

SUBMISSION CHECKLIST

- Cover letter to the editor
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  - Confirming that "the paper is not under consideration for publication in another journal".
  - Including disclosure of any commercial or financial involvement.
  - Confirming that the statistical design of the research article is reviewed.
  - Confirming that last control for fluent English was done.
  - Confirming that journal policies detailed in Information for Authors have been reviewed.
  - Confirming that the references cited in the text and listed in the references section are in line with NLM.
- Copyright Agreement Form
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- Permission of previous published material if used in the present manuscript
- Acknowledgement of the study "in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration.
- Statement that informed consent was obtained after the procedure(s) had been fully explained. Indicating whether the institutional and national guide for the care and use of laboratory animals was followed as in "Guide for the Care and Use of Laboratory Animals".
- Title page
  - The category of the manuscript
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  - Short title (running head)
  - All authors' names and affiliations (institution, faculty/department, city, country), e-mail addresses
  - Corresponding author's email address, full postal address, telephone and fax number
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- Main Manuscript Document
  - The title of the manuscript
  - Abstract 200-250 words
  - Key words: 3 - 6 words
  - Main article sections
  - References
  - Acknowledgement (if exists)
  - All tables, illustrations (figures) (including title, description, footnotes)

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