CLINICAL STUDY

CLINICAL APPEARANCES IN PATIENTS WITH NASOPHARYNGEAL MALIGNANCY: RETROSPECTIVE ANALYSIS

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SUMMARY

Aim: The aim of this study was to investigate the association between the results of nasopharyngeal (NPX) biopsies and clinical presentations in patients with suspected nasopharyngeal carcinoma, and also examine the association between nasopharyngeal carcinoma subtypes and clinical findings.

Material and methods: A retrospective study has been conducted at our institute to analyse 746 patients with nasopharyngeal biopsy. Clinical presentations and findings were analyzed to assess the association between benign and malignant biopsy outcomes. In addition, we further investigated malignant subgroups and clinical appearance.

Results: The benign and malignant groups comprised 639 (85.7%) and 107 (14.3%) patients, respectively. Neck mass (NM) and epistaxis were significantly higher in the malignant than in the benign group ($p < 0.001$, $p < 0.001$). Nasal obstruction (NO) and hearing loss were significantly higher in the benign group than in the malignant group ($p = 0.003$, $p = 0.008$). NM and OME were the most frequent findings in undifferentiated NPC (UNPC) (71.4%, 64%) respectively. NO was the most frequent symptoms in UNPC and lymphomas (31.3%, 25%). The sign that had the highest sensitivity was NM (45.8%). The sensitivity of all the symptoms and clinical signs was generally low.

Conclusion: Neck mass and OME are the most common findings in UNPC, whereas nasal obstruction and neck mass are the main symptoms and signs in lymphomas. The ability of neck mass, epistaxis, nasal obstruction and hearing loss to predict NP malignancy was limited.

Keywords: Nasopharyngeal carcinoma, neck mass, epistaxis, nasopharyngeal biopsy

NAZOFARENKS MALİGNİTELERİNDE KLİNİK BULGULAR: RETROSPEKTİF ANALİZ

ÖZET

Amaç: Nazofarenks karsinomu şüphesi olan hastaların biopsi sonuçları ile klinik bulguları arasındaki ilişkiyi ve nazofarenks karsinomu alt gruplarının klinik bulgularını araştırmak.

Yöntem ve gereçler: Kliniğimizde nazofarenks biopsisi yapılan 746 hastanın kayıtları retrospektif olarak incelendi.Malign ve benign gruplar arasında ilişkiyi değerlendirmek için klinik bulgu ve şikayetler karşılaştırıldı.Ayrıca malign alt gruplar ve klinik görünümleri araştırıldı.

Bulgular: Biopsi sonuçları 639(%85.7) benign, 107(%14.3) maligndi. Boyunda şişlik ve burun kanaması malign grupta benign gruptan anlamlı olarak yüksekti ($p < 0.001$, $p < 0.001$).Burun tıkanıklığı ve işitme kaybı ise benign grupta malign gruba göre anlamlı olarak yüksekti ($p = 0.003$, $p = 0.008$).Boyun şişliği olan hastaların %71.4'ü, otitis media saptanan hastaların % 64'ü andiferansiye nazofarenks karsinomuydu. Burun tıkanıklığı en fazla andiferansiye karsinom ve lenfomalarda görülmekteydi (31.3%, 25%).Sensitivitesi en yüksek olan bulgu boyunda şişlikdi (45.8%).Genel olarak tüm klinik şikayet ve bulguların sensitivitesi düşüktü.

Sonuç: Boyun şişliği ve otitis media andiferansiye karsinoma,burun tıkanıklığı ve boyun şişliği ise lenfomaların ana semptom ve bulgularıdır. Boyun şişliği, burun kanaması, burun tıkanıklığı ve işitme kaybının nazofarenks malignitelerini belirleyebilme yeteneği düşüktür.

Anahtar Sözcükler: Nazofarenks kanseri, boyunda kitle, burun kanaması, nazofarenks biopsisi

INTRODUCTION

Nasopharyngeal carcinoma (NPC), a nonlymphomatous squamous cell carcinoma originating from the superficial epithelium of the nasopharynx (NP), has a specific racial and geographical distribution. Specifically, it has a high prevalence in Southern China, Southeast Asia, and Taiwan, with the Middle East and North Africa as other common regions [1-3].

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It most commonly occurs in the fourth to sixth decades of life and is more prevalent in men than in women. According to the most recent histological classification of the World Health Organization (WHO) in 2005, epithelial NPCs are divided into three groups: keratinizing squamous cell carcinoma, nonkeratinizing squamous cell carcinoma and basaloid squamous cell carcinoma. The nonkeratinizing group is distinguished by two subtypes: differentiated and undifferentiated. Undifferentiated NPC (UNPC) is the most common type of NPC and is highly associated with the Epstein–Barr virus (EBV) in almost 100 % of cases.

Lymphoma originates from the subepithelial lymphoid cells of the extranodal lymphatic system of the tonsillapalatina and nasopharynx within the Waldeyer ring and is the second common malignancy in NP [4].

Wei and Sham distinguished the clinical signs and symptoms of NPC patients into four groups: 1) symptoms resulting from the tumor mass in the NP (nasal obstruction, epistaxis and nasal discharge), 2) symptoms and signs related to dysfunction of the eustachian tube (ET) [effusion with otitis media (OME), hearing loss], 3) symptoms resulting from extension towards the skull base (headache, diplopia, facial pain, and numbness), and 4) palpable neck masses [5]. The most common clinical findings in NPCs are a fast growing neck mass (frequently localized in the posterior neck triangle and upper jugular chain) (76 %); nasal symptoms including nasal obstruction, discharge, and epistaxis (73%); aural symptoms including OME, hearing loss, and tinnitus (62%); and symptoms associated with cranial nerve involvement (20%) [6].

Generally, all NPC patients are symptomatic at the time of diagnosis with approximately 1 % NPC patients being asymptomatic and diagnosed incidentally. There is no scale established for the subtype-specific symptoms and clinical signs of NPC, and no investigations related to this have been reported in the literature.

The aim of this study was to demonstrate the relationship between the clinical presentations and findings of patients with suspected NPC and to investigate whether the clinical findings correlate with NPC subtypes.

MATERIAL and METHODS

The files of 746 patients who underwent NP biopsy at İstanbul Training and Research Hospital Department of Otorhinolaryngology were retrospectively screened between 2005 and 2016. The protocol was approved by the institutional review board of the study was approved by the Local Ethics Committee of the Istanbul Training and Research Hospital (date:15.05.2015, number:641). The age, sex, initial presentations and findings (neck mass, epistaxis, nasal obstruction, OME, hearing loss, headache, and tinnitus) were recorded. Pathologic diagnoses were separated as benign and malignant. Clinical and demographic features between benign and malignant groups were compared. In addition, we further analyzed to assess the association between clinical findings and malignant tumor subtypes. Patients who had previously been diagnosed with NPC and recurrences; who were reported to have inadequate biopsy material; and those under 14 years of age were excluded from this study.

Statistical analyses were conducted using the SPSS 15.0 for Windows software package (SPSS, Inc.,Chicago,IL,USA). Descriptive statistics; mean, standard deviation, minimum, maximum for numerical variables, categorical variables were given as number and percentage. As the numerical variable in the independent two groups didn't satisfy the normal distribution condition, the comparison was made with the Mann Whitney U test. The chi-square test was utilized for between groupcomparison of categorical variables. Monte Carlo simulation test was applied when conditions were not obtained. Risk effects were analyzed by logistic regression analysis. A p value of less than 0.05 was considered statistically significant. Tests were conducted with a 95% CI.

RESULTS

The subjects were divided into two groups according to their biopsy results: 639 were in the benign group (85.7%) and 107 (14.3%) were in the malignant group. The mean age of the benign group was 42 (14-88) years; the mean age of the malignant group was 55.6 (18–85) years. The mean age of the malignant group was statistically higher than that of the benign group ($p < 0.001$). The prevalence of clinical symptoms and signs for both groups are shown in Table 1. Neck mass and epistaxis were significantly higher in the malignant than in the benign group ($p < 0.001$ and $p < 0.001$, respectively). When nasal obstruction was combined with other signs, it was significantly higher in the malignant group than in the benign group ($p<0.001$, $p=0.003$, $p=0.020$, and $p=0.020$, respectively). Nasal obstruction and hearing loss were significantly higher in the benign group than in the malignant group ($p = 0.003$ and $p = 0.008$). OME was higher in the malignant group than in the benign group, but the difference was not statistically significant (Table 1).

Reactive lymphoid hyperplasia (57.3%) and chronic inflammation (39.4%) were the most common results in the benign group. UNPC (57.9%), differentiated squamous carcinoma (DNPC) (21.5%), and lymphomas (12.1%) were the most common subtypes in the malignant group (Table 2). Analysis of the frequency of symptoms and clinical findings in malignant tumor subtypes revealed nasal obstruction to occur most frequently in the patients with UNPC, lymphomas and DNPC (31.3%, 25%, 18.8 % respectively). Neck mass was most frequently seen in patients with UNPC (71.4%). Headache and OME were most frequently seen in patients with UNPC and

DNPC, and epistaxis was most frequently seen in patients with UNPC (63.6%) (Table 3).

Univariate logistic regression analyses showed significant differences in neck mass (odds ratio (OR), 4.960; 95% CI, 3.197–7.696; p<0.001), epistaxis (OR,10.345; 95% CI,3.915–27.335; p<0.001), nasal obstruction (OR,0.517; 95% CI,0.332–0.804; p=0.003), and hearing loss (OR,5.541;95%CI,1.334–23.007;p=0.018) (Table 4). The evaluation of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of clinical symptoms and signs is shown in Table 5. Among them, neck mass showed the highest sensitivity (45.8%) but the sensitivity of all the symptoms and clinical signs was generally limited. The PPV and the accuracy of epistaxis had the highest sensitivity among the other variables (61.1% and 86.2%, respectively) (Table 5). These analyzes were performed to determine findings that could predict malignancy.

Table 1. Comparison of the clinical and demographic features between benign and malignant groups.

		Benign n=639 (%85,7)		**Malignant n=107 (%14,3)**		
		Mean.±SD	**Min-Max**	**Mean.±SD**	**Min-Max**	**p**
Age		42,0±17,8	14-88	55,6±13,3	18-85	<0,001
		n	**%**	**n**	**%**	
Symptoms		617	96,6	107	100	0,059
	NO	289	45,2	32	29,9	0,003
	Neck mass	93	14,6	49	45,8	<0,001
	Epistaxis	7	1,1	11	10,3	<0,001
	Headache	28	4,4	4	3,7	1,000
	Tinnutus	7	1,1	0	0,0	0,602
	OME	127	19,9	25	23,4	0,407
	Hearingloss	61	9,5	2	1,9	0,008
	Disfagia	2	0,3	0	0,0	1,000
	Other	4	0,6	3	2,8	0,065
	NO+Neckmass	0	0,0	6	5,6	<0,001
	NO+ Epistaxis	0	0,0	3	2,8	0,003
	NO+Headache	0	0,0	2	1,9	0,020
	NO+OME	0	0,0	2	1,9	0,020
	NO+Epistaxis+OME	0	0,0	1	0,9	0,143

NO: nasal obstruction, OME= otitis media with effusion

Table 2. Distribution of patients corresponding of biopsy results.

		Benign	
		n	%
Result of biopsy	Reactive lymphoid hyperplasia	366	57,3
	Chronic inflammation	252	39,4
	Thornwaldt'scyst	5	0,8
	Granulomatous lesion	6	0,9
	Actinomyces	3	0,5
	Acut inflammation	3	0,5
	Other	4	0,6
		Malignant	
		n	%
Result of biopsy	Undifferantiated squamous carcinoma	62	57,9
	Differantiated squamous carcinoma	23	21,5
	Lymphoma	13	12,1
	Keratinizing carcinoma	3	2,8
	Other	6	5,6

Table 3. Distribution of clinical symptoms according to tumor classifications

Malignant tumors subtypes		NO	NM	Epistaxis	Headache	OME	Hearing loss
Undifferantieted carcinoma	n	10	35	7	2	16	2
	%	31,3	71,4	63,6	50,0	64,0	100
Differantiated carcinoma	n	6	7	1	2	8	0
	%	18,8	14,3	9,1	50,0	32,0	0,0
Keratinizing carcinoma	n	3	0	1	0	0	0
	%	9,4	0,0	9,1	0,0	0,0	0,0
Lymphoma	n	8	7	1	0	1	0
	%	25,0	14,3	9,1	0,0	4,0	0,0
Other	n	5	0	1	0	0	0
	%	15,6	0,0	9,1	0,0	0,0	0,0

Table 4. The univariate regression analysis of clinical symptoms in determination of malignite

	p	OR	95% C.I.
Nasal obstruction	0,003	0,517	0,332
Neck mass	<0,001	4,960	3,197
Epistaxis	<0,001	10,345	3,915
Headache	0,761	0,847	0,291
Otitis media with effusion	0,407	1,229	0,754
Hearing loss	0,018	5,541	1,334

Table 5. Screening performance and corresponding 95% CI of clinical signs and symptoms

		Sensitivity	Specificity	PPV	NPV	Accuracy
Symptoms and signs		%	%	%	%	%
	NO	29,9	54,8	10,0	82,4	51,2
	Neckmass	45,8	85,4	34,5	90,4	79,8
	Epistaxis	10,3	98,9	61,1	86,8	86,2
	Headache	3,7	95,6	12,5	85,6	82,4
	OME	23,4	80,1	16,4	86,2	72,0
	Hearing loss	1,9	90,5	3,2	84,6	77,7

NO:nasal obstruction, OME:otitis media with effusion

DISCUSSION

Nasopharyngeal carcinoma can be diagnosed early by rapidly initiating an endoscopic examination, imaging, and biopsy in the suspected cases. Tumor growth occurs primarily in the pharyngeal recess (Rosenmüller's fossa) in the lateral wall of the nasopharynx, and secondarily in the superior posterior wall. However, the symptoms may be nonspecific in the early stages, so the diagnosis of most patients is delayed by about six months [7]. For an early diagnosis of NPC, the history, signs, and clinical findings must be carefully evaluated, and a clinical examination must be made to avoid overlooking suspicious lesions in the nasopharynx. Nasal endoscopy plays a crucial role in NPC diagnosis. In cases where the tumor cannot be clearly visualized endoscopically, a slight fullness and asymmetry with pulling may be detected. Video nasopharyngoscopes and fiber optic scopes have developed resolution and supply a larger field of view and have recently used widely [8].

The sensitivity of diagnostic accuracy of MRI for NPC is to be higher than 90 % [9-10].Early-stage submucosal tumors can be separated from normal mucosa as hypointense with gadolinium MRI. In such cases, the patients should undergo biopsy with endoscopy [11-13].If computed tomography (CT) scan (neck, sinus or head) performs, radiologist likely should focus on the nasopharynx. Otherwise, the high false-negative rate is likelihood [8]. 18-fluoro-2-deoxyglucose (FDG) positron emission tomography (PET) is useful tool in distinguishing recurrent NPC lesions especially [11]. Narrow-band imaging (NBI) endoscopy as a novel technique that enhances the diagnostic sensitivity especially for adult nasopharyngeal lymphoid tissue hyperplasia has significant screening performance [14]. Some biology markers in the nasopharyngeal swabs confirm predicting and screening the newly diagnosed NPC and mucosal recurrences NPC (eg, Ebstein-Barr virus latent membrane protein 1 (EBV LMP-1) gene andEbstein-Barr nuclear antigen gene (EBNA)). Hao et al concluded that nasopharyngeal swab coupled with EBV LMP-1and EBNA detection could serve as a good supplement to pathologic diagnosis of NPC [15].

Hsieh et al reported that the positive rate of all NP biopsies was 30.1 % in 512 NP biopsies in Taiwan [13]. On the contrary, in the present study, 85.7% of patients who underwent nasopharyngeal biopsy were reported as having a benign pathology, whereas 14.3% had malignant tumors. The high rate is may be explained by the fact that Taiwan is an endemic region for NPC.

Berkiten et al. reported that nasal obstruction was the most common symptom in their study. Hearing loss and neck mass were the other main symptoms in 1647 adult patients with nasopharyngeal pathology. In the same study, malignant pathologies showed a significant increase with age [16]. In the present study, nasal obstruction and OME were the most common symptoms in the benign group, with reactive lymphoid hyperplasia as the most common benign diagnosis. This demonstrates that adenoid tissue is an important cause of nasal obstruction in the adult age group, despite its regression in adult age. A significant difference was also noted in terms of age between the malignant and benign groups in the current study.

In the univariate analyses of the current study, neck mass and nasal obstruction were the most significant clinical findings of all variables in the malignant group of patients (odds ratio (OR), 4.960; 95% CI, 3.197–7.696; $p<0.001$), epistaxis (OR,10.345; 95% CI,3.915–27.335; $p<0.001$). Hsieh et al found that neck mass was the second significant clinical finding in the patients with newly diagnosed NPC and reported a sensitivity rate of 66% [13]. Skinner et al reported that neck mass was the most common findings of nasopharyngeal carcinomas, but 70% of their patients were in advanced stages of the disease [17]. Similar to the results in the literature, in the present study, the neck mass was the most common initial presenting finding in the malignant group and had a limited sensitivity (45.8%). The specificity, PPV, NPV, and accuracy for neck mass were calculated as 85.4, 34.5, 90.4, and 79.8%, respectively. In the current study, no significant difference was found between the benign and malignant groups in terms of OME prevalence ($p=0.407$). Similarly, Hsieh et al found no significant difference between their cancerous and noncancerous groups [13]. This lack of difference may often be a result of the association between OME and postnasal discharge in the benign group. It also shows that adenoid tissue should be taken into account, especially in cases of unilateral OME [18]. Adham et al. reported that most of their patients (60.6%) had unilateral ear problems as the earliest sign of NPC in Indonesia [19]. NPC is known to cause OME via obstruction in the ostium of ET and further infiltration of the tensor veli palatini muscle. Careful evaluation of the nasopharynx is therefore necessary to exclude NPC in the presence of unilateral, unexplained OME in an adult patient.

The analysis of NPC subtypes revealed that UNPC (57.9%) was the most common subtype, followed by DNPC (21.5%) and lymphomas (12%). To the best of our knowledge, this is the first study to investigate the relationship between clinical findings and NPC subtypes. Neck mass and OME were the most common findings in UNPC. Similarly, OME and neck mass were the most frequent signs in DNPC initially. UNPC has a higher incidence of local tumor control rate compared to DNPC but higher incidence of metastasis [20,21]. In these types of tumors, neck mass often presents as a sign of late stage NPC. On the contrary, nasal obstruction and neck mass are the main symptoms and clinical findings in lymphomas due to simultaneous tumor progression in other extranodal lymphoid tissues of the Waldeyer'sring, it may congest the posterior choana and nasopharynx and cause nasal obstruction. Epistaxis was detected mostly in UNPC. The incidence of headache and hearing loss was generally low in all malign subtypes.

This study has several limitations. First, its small size, second, is a retrospective nature. Finally, the study was conducted at a single institution in a limited geographic region.

CONCLUSION

NPC is one of the most easily misdiagnosed tumors because it presents initially with nonspecific symptoms and signs. Neck mass and OME are the most common findings in UNPC, whereas nasal obstruction and neck mass are the main symptoms and signs in lymphomas. The ability of neck mass, epistaxis, nasal obstruction, and hearing loss to predict NP malignancy was limited. Hence, it may that there is no effective screening process yet. In particular, patients over 50 years of age with epistaxis and nasal obstruction should undergo careful examination of the nasopharynx by endoscopy and even if there is no clear tumor, a biopsy is still absolutely necessary. Larger sample size involving a greater number of patients and nasopharyngeal malignancy subtypes is required to confirm our study results.

Compliance with Ethical standards

Informed consent:

Additional informed consent was obtained from all individual participants for whom identifying information is included in this article.

Ethical Approval:

All procedures performed in studies involving human participants were in accordance with the ethical standards of the Local Ethics Committee of the Istanbul Research and Training Hospital and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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Conflict of Interest:

The authors declare that they have no conflict of interest.

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