

The diagnosis of sinonasal lymphoma: a challenge for rhinologists

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Abstract The presenting symptoms of sinonasal lymphoma are usually similar to those of benign inflammatory diseases. Adequate amount of biopsy tissue is required for a definitive diagnosis because tumor coexisting with necrosis or inflammation is not uncommon. Therefore, the diagnosis of sinonasal lymphoma is a challenge for rhinologists. Thirty-two patients diagnosed as having sinonasal lymphoma from 1990 to 2010 in our hospital were included in this study. The presenting symptoms of these patients included nasal obstruction, rhinorrhea, bloody discharge/epistaxis, post nasal drip, facial swelling, neck mass, orbital symptoms, fever, and body weight loss. The average period between patients' awareness of their symptoms and their decision to seek medical help was 8.9 months. When they were referred to our hospital, the first impression of 20 patients (62.5%) was benign or malignant nasal neoplasm, and that of the other 12 patients

(37.5%) was rhinitis or rhinosinusitis. These patients then received image studies and biopsy or surgical intervention. Most patients needed repeated biopsies, endoscopic sinus surgery, turbinectomy, or Caldwell-Luc operation for a definitive diagnosis. Their histopathologic classification included NK/T cell lymphoma ($n = 13$, 40.6%), peripheral T cell lymphoma ($n = 12$, 37.5%), and diffuse large B cell lymphoma ($n = 7$, 21.9%). Peripheral T cell lymphoma and NK/T cell lymphoma mostly occurred in the nasal cavity, whereas sinus involvement without nasal disease is common in B-cell lymphoma. Our results reveal that patients with sinonasal NHL tend to ignore their symptoms until they become serious, and a definitive diagnosis usually requires repeat and deep biopsy.

Keywords Sinonasal lymphoma · Extranodal lymphoma · Non-Hodgkin's lymphoma · Sinonasal tract

This study was approved by the Institutional Review Board of Taichung Veterans General Hospital.

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Introduction

Hodgkin's lymphoma rarely arises outside lymph nodes, whereas more than 60% of non-Hodgkin lymphoma (NHL) of the head and neck occurs in extranodal sites including paranasal sinuses, nasal cavity, oral cavity, oropharynx, and laryngopharynx [1]. Sinonasal NHL is a rare form of extranodal lymphoma in the Western population, representing less than 0.5% of all cases [2]. However, the sinonasal tract is the second most common site of the extranodal lymphoma in Asia [3, 4]. As previous reports from other Asian countries have indicated [5, 6], sinonasal NK/T or T cell lymphomas are more common than B cell lymphoma in Taiwan [7, 8].

Because of the relatively low incidence of NHL, its precise clinical characteristics have not been fully

understood. The presenting symptoms are usually similar to those of benign inflammatory diseases, making the diagnosis of sinonasal NHL difficult [9–11]. The primary role of rhinologist in sinonasal NHL is diagnosis and follow-up observation of the primary sites. Early diagnosis and referral to an oncologist help improve the prognosis in this aggressive disease [4]. Previous reports have indicated that early-stage nasal lymphoma has a significantly better prognosis [12–14]. However, previous studies of sinonasal lymphoma were mostly focused on its histopathology findings or treatment outcomes. Few articles examined the clinical characteristics and diagnostic techniques [4, 15, 16]. The purpose of this study was to identify pitfalls in diagnosis of sinonasal NHL by reviewing the diagnostic scheme in our patients with sinonasal NHL.

Materials and methods

A retrospective review was conducted at the Department of otolaryngology of Taichung Veterans General Hospital (TCVGH), Taiwan. Patients diagnosed as having sinonasal NHL from 1990 to 2010 were included in this study. Patients whose NHL arose from other aerodigestive tract sites including the nasopharynx, palatine tonsil, tongue base, oropharynx, and oral cavity were excluded. Patients without complete clinical or histopathology data were also excluded. This study was approved by the Institutional Review Board of TCVGH.

The demographic data, presenting symptoms, first impression, image findings, tumor stage, treatment modalities, and outcome were analyzed by chart review. All cases had available hematoxylin and eosin (H and E) and immunohistochemistry (IHC) stained slides for review. IHC stains were done depending on the morphology and phenotype of neoplastic cells from H and E stained slides, including AE1/AE3, CD3, CD20, CD56, CD79a, CD4, CD8, UCHL1, and Ki-67. Epstein–Barr virus was detected using in situ hybridization (ISH) with Epstein–Barr virus encoded small RNA (EBER) probes. Histopathological classification was determined according to the World Health Organization classification of neoplasms of the hematopoietic and lymphoid tissues [17]. The histopathology diagnosis and classification were confirmed by our coauthor (Wang, R.C., a senior pathologist). Tumor staging system was based on the Ann Arbor classification of malignant lymphoma [18].

Results

Thirty-two patients were enrolled in this study. There were 22 males and 10 females, and the average age was

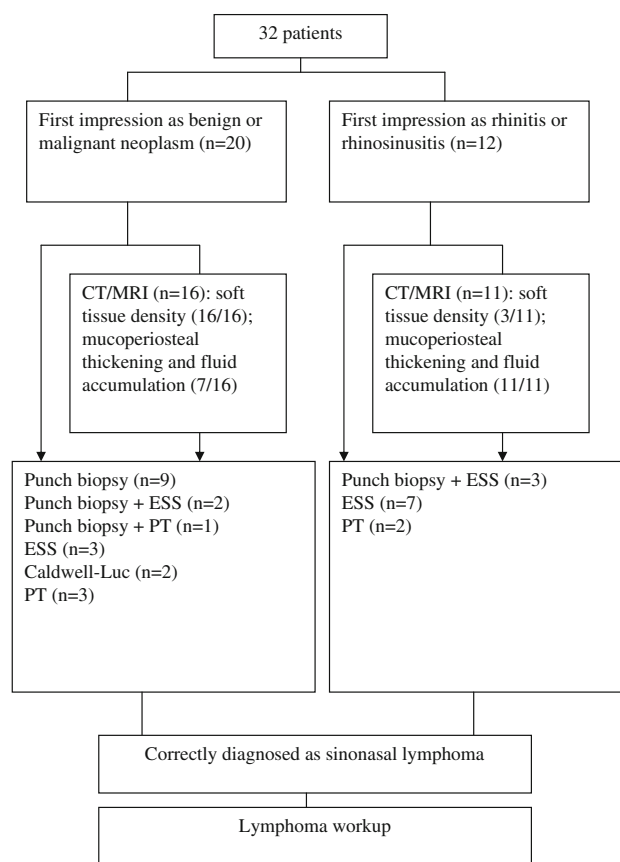
56.3 years. The presenting symptoms of these patients included nasal obstruction, rhinorrhea, bloody discharge/epistaxis, facial swelling, orbital symptoms, post nasal drip, body weight loss, neck mass, and fever. Sixteen patients (50%) presented with more than one symptom. Among those symptoms, nasal obstruction was the most common one. The duration between patients' awareness of their symptoms and their decision to seek medical help ranged from 1 week to 4 years, with a mean of 8.9 months. When they were referred to our hospital, the physical examination revealed mass lesion in nasal cavity, nasal discharge, enlarged inferior turbinate, deviated nasal septum, facial swelling or neck mass. Eighteen patients were found to have mass lesions in their nasal cavities. According to the chart records, the appearance of the mass lesions included ulcerative, polypoid, granuloma-like or submucosal change. The first impression of 20 patients (62.5%) was benign or malignant nasal neoplasm and that of the other 12 patients (37.5%) was rhinitis or rhinosinusitis. The clinical characteristics of these patients are summarized in Table 1.

Twenty patients who had a first impression of nasal tumor then received image studies, computed tomography (CT) or magnetic resonance imaging (MRI), and biopsy procedures. Image studies were available for 16 patients when we conducted this review (12 patients received CT, 1 received MRI, and 3 received both CT and MRI): sinonasal soft tissue mass with or without bony erosion was found in all films, secondary mucoperiosteal thickening, and fluid accumulation in nasal cavity or sinuses was noted in seven CT/MRI films. Among these 20 patients, 9 patients had a definite pathological diagnosis by punch biopsy of nasal cavity lesion (4 received biopsy once and 5 received biopsy twice); 3 patients did not have a definitive diagnosis by punch biopsy and then received partial inferior turbinectomy (PT) or endoscopic sinus surgery (ESS) for harvest deep tissue; 5 patients received ESS or Caldwell–Luc operation because image studies showed tumor was mainly located within sinus cavities; and 3 patients received PT for diffuse submucosal/mucosal change of inferior turbinate. Among the 12 patients who had a first impression of rhinitis or rhinosinusitis, 11 had image studies (6 received CT, 1 received MRI, and 4 received both CT and MRI). All 11 CT/MRI films showed sinonasal mucosal thickening, fluid accumulation in sinuses, and 3 revealed sinonasal soft tissue density. These patients then received surgical procedure under the indication of medical treatment failure for rhinitis/rhinosinusitis. Three patients received punch biopsies and then ESS (biopsies showed inflammation); two patients received PT and correction of deviated septum, and seven received ESS. The diagnostic scheme of all 32 patients is shown in Fig. 1. The representative rhinoscope and image findings from three patients are

Table 1 The clinical characteristics of patients

Characteristics		
Age (median)	56.3	years
Gender (male/female)	22/10	
Presenting symptoms	<i>N</i>	<i>%</i>
Nasal obstruction	24	75
Rhinorrhea	10	31.2
Bloody discharge/epistaxis	6	18.9
Facial swelling	3	9.4
Orbital symptoms (ptosis, limitation of eye movement, visual loss)	4	12.5
Post nasal drip	3	9.4
Body weight loss	3	9.4
Neck mass	1	3.1
Fever	1	3.1
Physical findings		
Nasal cavity mass lesion	18	56.25
Nasal discharge	6	18.75
Enlarged inferior turbinate (unilateral/bilateral)	5	15.25
Facial swelling	3	9.4
Deviated nasal septum	2	6.3
Neck mass	1	3.1
First impression		
Nasal tumor	60	62.5
Rhinitis/rhinosinusitis	12	37.5
Ann Arbor stage		
I	24	75
II	4	12.5
III	0	0
IV	4	12.5

demonstrated in Fig. 2. A 69-year-old male presented with right nasal obstruction and rhinorrhea for 3 months. He had a nasal tumor growing from right inferior turbinate and received punch biopsy (Fig. 2a). Coronal CT section shows soft tissue filling in his right nasal chamber and secondary maxillary sinusitis (Fig. 2b). Another 73-year-old female presented with left nasal obstruction and bloody rhinorrhea caused by a large B cell lymphoma. Anterior rhinoscopy revealed diffused mucosal change of left inferior turbinate and bloody discharge (Fig. 2c). Coronal CT section showed soft tissue filling in her left nasal chamber and secondary maxillary sinusitis (Fig. 2d). She received left PT to harvest tissue and relief from severe nasal obstruction. The third patient was a 62-year-old female with nasal obstruction, rhinorrhea, and post nasal drip. Anterior rhinoscopy revealed bilateral diffused mucosal edema and nasal discharge (Fig. 2e). Coronal CT section showed bilateral hypertrophic inferior turbinates and maxillary sinusitis (Fig. 2f). She was initially misdiagnosed as chronic rhinosinusitis and received ESS.

**Fig. 1** The diagnostic scheme of 32 patients with sinonasal lymphoma. *CT* computed tomography; *MRI* magnetic resonance imaging; *ESS* endoscopic sinus surgery; *PT* partial inferior turbinectomy

The pathological examination of sinonasal tissue revealed diffused large B cell lymphoma.

The histopathologic classification of our patients included NK/T cell lymphoma ($n = 13$, 40.6%), peripheral T cell lymphoma ($n = 12$, 37.5%) and diffuse large B cell lymphoma ($n = 7$, 21.9%). Figure 3a demonstrates sections from a nasal cavity NK/T cell lymphoma: H and E stained slide shows atypical lymphocytes, plasma cells and eosinophilic infiltration in nasal mucosa; IHC stained slides show the atypical lymphocytes expressed cytoplasmic CD3 and membranous CD56; ISH stained slide shows neoplastic cells expressed nuclear EBER. Figure 2b demonstrates sections from a nasal cavity peripheral T cell lymphoma: H and E stained slide shows atypical lymphocytes and plasma cells infiltration in nasal mucosa; IHC stained slides show lymphocytes expressed cytoplasmic CD3 and membranous CD56; ISH stained slide does not show expression of nuclear EBER. Figure 3c demonstrates sections from a nasal cavity diffuse large B cell lymphoma: H and E stained slide shows large tumor cells with moderate amount of cytoplasm. The nuclei are large with the presence of vesicular chromatin and distinct nucleoli. Brisk mitotic activities and apoptotic figures are also noted.

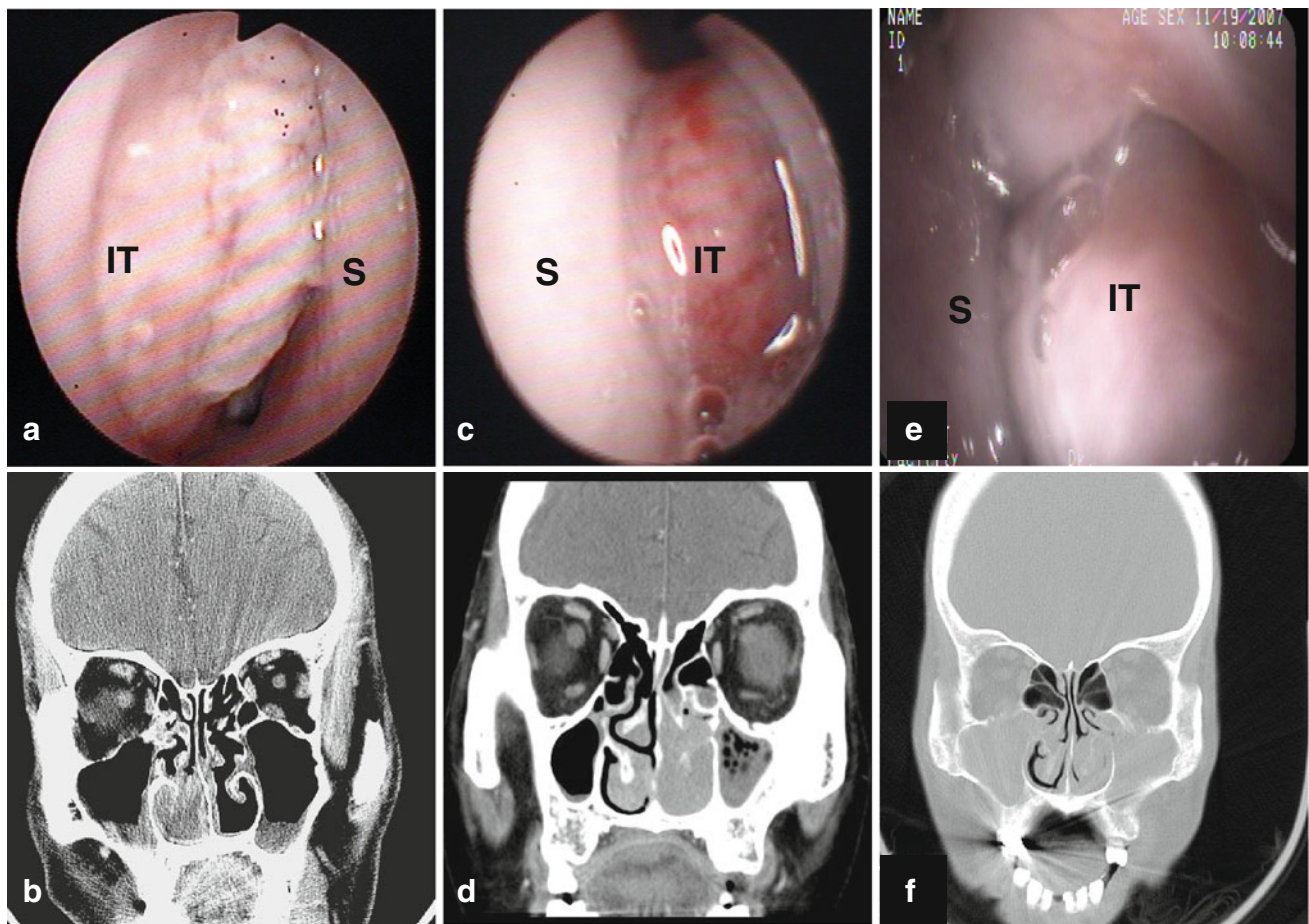


Fig. 2 The rhinoscope and image findings shown from a patient with peripheral T cell lymphoma (**a, b**) and two patients with diffused large B cell lymphoma (**c–f**). *IT* inferior turbinate; *S* septum

Diffuse strong membranous pattern of CD20 in IHC slide indicates the B cell phenotype of this tumor. IHC stain for CD10 shows that tumor cells do not express the follicular center marker. The fraction of Ki-67-positive tumor cells (the Ki-67 labeling index, often correlated with the clinical course of cancer) is about 60–70% in this case.

Lymphoma located at paranasal sinus or showing sinonasal extension was mainly diffuse large B-cell lymphoma (Table 2). The average duration between the first clinic visit and a definitive diagnosis was 53 days. According to the Ann Arbor classification, 24 patients were stage I, 4 were stage II, and 4 were stage IV. The primary tumor involved nasal cavity in 14 patients, paranasal sinuses in 2, and both nasal cavity and paranasal sinuses in the other 16. Seven patients (21.9%) had tumor involvement of the bilateral nasal cavities. Three patients did not receive further treatment at our hospital. Six patients received radiotherapy, 13 patients received chemotherapy, and 10 patients received chemotherapy and radiotherapy. At the end of this study, 3 patients were lost to follow-up, 11 patients died, and 18 patients were alive.

Discussion

Sinonasal NHL develops gradually within a confined anatomic space; therefore, the initial signs and symptoms of this disease are known to be subtle and often mimic those of benign inflammatory diseases [19, 20]. The average period between our patients' awareness of their symptoms and their decision to seek medical help was 8.9 months. This indicates that patients tend to ignore their symptoms until they become serious. Twelve patients (37.5%) in this study presented an initial impression of rhinitis/rhinosinusitis when they were first referred to a rhinologist. It seems that the clinical presentations of sinonasal lymphoma and the results of physical examination can be confusing; even rhinologists may miss the diagnosis. Alerting symptoms continue to develop until the neoplasm reaches a considerable size or involvement of the adjacent anatomic structures occurs. However, only a few of our patients presented with orbital symptoms (12.5%), facial swelling (9.4%), body weight loss (9.4%), neck mass (3.1%), and fever (3.1%). The incidence of systemic B

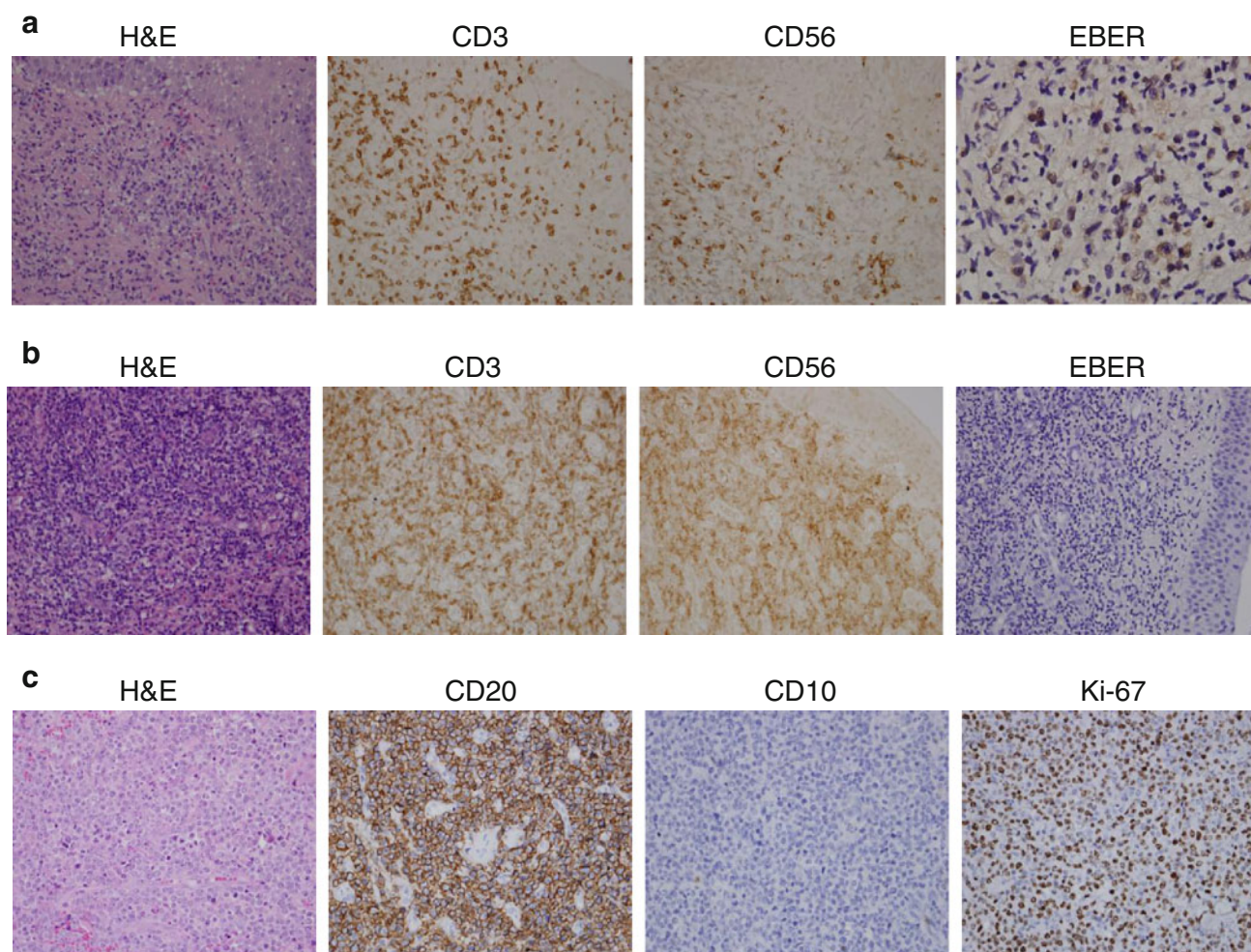


Fig. 3 The hematoxylin and eosin (H and E), *IHC* immunohistochemistry, *ISH* in situ hybridization stained slides of sections from a nasal cavity NK/T cell lymphoma (**a**), a peripheral T cell lymphoma (**b**), and a diffuse large B cell lymphoma (**c**). *H and E* hematoxylin

and eosin; *EBER* Epstein-Barr virus encoded RNA (H and E stain 400×; *IHC* stain for CD3, CD56, CD20, CD10, and Ki-67 400×; *ISH* stain for *EBER* 1000× in panel A and 400× in panel B)

Table 2 Histological types and tumor location

Histological type	Tumor location			Number
	Nasal cavity	Sinuses	Both	
NK/T cell	7	1	5	13 (40.6)
Peripheral T cell	6	0	6	12 (37.5)
Diffuse large B cell	0	1	6	7 (21.9)
Total	13	2	17	32 (100)

symptoms is believed to be low in sinonasal NHL [4, 21] and only one of our patients had B symptoms.

The rhinological findings of these patients varied. Most of our patients had nasal obstruction and presented with nasal mass lesions. The appearance of the mass lesions included ulcerative, polypoid, granuloma-like or submucosal change. NK/T cell lymphoma is known to destroy

nasal and palatal tissue and hence was called “lethal midline granuloma syndrome” in the past for this clinical entity [21, 22]. However, none of our patients presented with palatal or septal perforation when they first visited our department. Three patients with NK/T cell lymphoma developed palatal perforation afterwards. Secondary rhinosinusitis causing nasal discharge and mucosal swelling was common in our patients, and a surprising number of our patients were initially diagnosed as having rhinitis or rhinosinusitis. The image findings of these patients mostly confirmed the results of physical examination. Patients suspected of having tumor growth were found to have soft tissue density in their CT/MRI, while patients initially diagnosed as having rhinitis/rhinosinusitis had CT/MRI findings compatible with sinonasal inflammatory changes. In general, MRI is better than CT in the demonstration of tumor lesion. The sinonasal mucosal thickening can be

better differentiated from tumor via T2-weighted MRI when compared with CT scans [23]. However, the CT and MRI features are not specific and share similar findings with other aggressive nasal diseases [23, 24].

Repeated biopsy procedures were usually necessary to obtain adequate tissue for diagnosis of sinonasal lymphoma. Simple punch biopsy through nasal cavities did not harvest adequate amount of tissue in most patients. Surgical management such as ESS, PT, or Caldwell-Luc techniques was useful for harvesting adequate amount deep tissue for pathological examination. The possible explanations for the difficulty in harvesting adequate biopsy tissue in these patients are (1) sinonasal lymphoma frequently coexists with secondary rhinosinusitis, and (2) NK/T cell lymphoma tends to destroy adjacent anatomic structures. As a result of these two phenomena, the involved mucosa was interspersed with necrosis and inflammatory cells, making the diagnosis difficult [25]. Besides, lymphoma occasionally presented with a submucosal lesion, rather than the ulcerative mass appearance of squamous cell carcinoma. Superficial biopsy is not adequate for approaching deep-seated lesion. When making a decision on which biopsy method needs to use, the location of lesion and the ability to harvest adequate amount of tissue must be taken into consideration. ESS was chosen for biopsy in many of our patients since most of them had tumor that occupied both the nasal cavity and sinuses, and some patients were initially misdiagnosed as having rhinosinusitis. Caldwell-Luc operation was chosen for patients whose tumor mainly located in maxillary sinus or had invaded surrounding soft tissue. PT and correction of deviated nasal septum was a common procedure for relief of chronic nasal obstruction. Two of our patients initially misdiagnosed as chronic rhinitis had their diagnosis revised after histopathologic examination of the excised nasal tissue. The other three patients who were suspected having tumor over inferior turbinate received PT for diffuse submucosal/mucosal lesion over the inferior turbinate. Turbinectomy was sometimes chosen for diagnosing tumor origin from inferior turbinates because it can both obtain adequate tissue and relieve symptom of nasal obstruction [26, 27]. Sakamoto et al. [16] have suggested that the lateral plate of the nasal cavity and the inferior turbinate were the optimal sampling site for patients with NK/T cell lymphoma.

When comparison was made between patients with T or B cell lymphoma, our patients with T cell lymphoma were overall younger than those with B cell lymphoma (53.8 vs. 65.3 years). In addition, peripheral T cell lymphoma and NK/T cell lymphoma mostly occurred in the nasal cavity. Our results are in agreement with the finding of a previous study showing that the nasal cavity is more frequently the site of T cell and NK/T cell lymphoma, whereas sinus

involvement without nasal disease is common in B-cell lymphoma [28]. Our patients with T cell lymphoma were mostly diagnosed as having stage I disease, while patients with B cell lymphoma were often diagnosed at late stage (84.6% stage I in NK/T cell, 91.7% stage I in peripheral T vs. 28.6% stage I in B cell). A possible explanation is that T cell lymphoma located in the nasal cavity results in nasal symptoms earlier, whereas B cell lymphoma hiding in sinuses induces symptoms only after extension to surrounding structures.

Conclusion

The clinical manifestations of sinonasal NHL often mimic refractory rhinosinusitis. Patients with sinonasal NHL tend to ignore their symptoms until they become serious. The physical and radiological examinations of these patients are mostly non-specific. Thus, repeated deep biopsy is usually needed for a definitive diagnosis. Rhinologists should be alert to this aggressive diagnosis and consider it as one of the differential diagnoses of refractory rhinosinusitis. Early diagnosis and referral to an oncologist could improve the prognosis.

Conflict of interest None.

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