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Case Report
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Primary Laryngeal Lymphoma: A Rare Case Report and Clinical Characteristics in Chinese Patients

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Abstract

Purpose: Primary laryngeal lymphoma is rare. To characterize the clinical features of this disease, we describe in detail a case of a natural killer T-cell lymphoma originating in the larynx. In addition, we performed a retrospective study of laryngeal lymphoma cases published in the Chinese language literature.

Materials and Methods: In our case study, we present the disease, disease history, personal history, family history, physical examinations, imaging investigations, and histopathological examinations, while the age, gender, symptoms, involvement site, pathological subtype, disease course, tumor morphology, treatment, follow-up, and outcomes are analyzed in the Chinese literature study.

Results: A total of 62 articles comprising 90 cases were included. The average patient age was 45, with a male-to-female ratio of 7:3. Hoarseness was the most common initial symptom. The majority of cases originated in the supraglottis and were derived from B cells. Because of the non-specific nature of the clinical manifestations and imaging scans, the diagnosis and further typing of laryngeal lymphomas depend on histopathological examination and immunohistochemistry.

Conclusion: Therefore, physicians should consider performing a biopsy when laryngeal neoplasms are encountered to ensure that the correct diagnosis is made.

Keywords: Laryngeal lymphoma; Retrospective study; Chinese patients; Diagnosis

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Introduction

Lymphomas that originate in the larynx are very rare and only account for <1% of all laryngeal neoplasms [1]. Among them, Non-Hodgkin's Lymphoma (NHL) predominates, and the majority are of B cell origin [2,3]. Natural Killer (NK)/T-cell lymphoma, which is extremely rare, comprises only 2% to 20% of NHLs [4,5]. In addition, the presence of follicular lymphoid tissue makes the supraglottic structure a typical initiation site and the glottis and subglottis less common sites [6]. Currently, there are only a few published reports of primary NK/T-cell lymphomas of the larynx.

As the most populous country in the world, China could expect to have more cases of rare disease; and because of many differences with Western countries, such as geographical location, genetic factors, and lifestyle habits, laryngeal lymphomas in Chinese patients may have distinct clinical characteristics. In this article, we present a highly unusual case of a primary NK/T-cell lymphoma that originated in the vocal folds and mimicked the clinical features of a laryngeal squamous cell carcinoma. We have provided a highly comprehensive and detailed description of a laryngeal lymphoma regarding multiple aspects, including chief symptom complaint, present disease, history of past disease, personal history, family history, physical examination data, Computed Tomography (CT) examinations, Magnetic Resonance Imaging (MRI) examinations, electronic laryngoscopy examinations, immunohistochemical staining data, and whole-body Positron Emission Tomography (PET)-CT examinations. Moreover, we also retrospectively investigated Chinese language articles on primary laryngeal lymphomas to more fully understand this rare disease.

Materials and Methods

Studies were retrieved from the three largest and most commonly used Chinese-language databases: China National Knowledge Infrastructure, Wanfang, and Weipu. The search terms were 'larynx', 'laryngeal', 'vocal cord', 'glottic', and 'lymphoma'. Through the initial screening of the title and abstract, irrelevant articles were excluded. Remaining articles were then examined carefully. Articles that did not provide the necessary case information were excluded from the analysis. Studies were included if they provided information for at least patient age, gender, symptoms, and

pathological result. We also analyzed the following clinical features, if available: Disease course, involvement site, tumor morphology, treatment, follow-up, and outcome. In addition, smoking history was also summarized for each gender.

Results

Case report

A 70-year-old man who had a greater than 2-month history of progressive hoarseness was referred to our hospital. The patient also reported coughing but without pain, expectoration, hemoptysis, dysphagia, and dyspnea. He did not experience fever, night sweats, insomnia, or weight loss. He visited a local hospital and was prescribed antibiotics with little improvement. The patient was addicted to tobacco and alcohol, with a 50-year history of smoking about 2 packs/day and a 40-year history of drinking about 0.5 liters of liquor/day. According to his medical history, he had been diagnosed with hypertension 10 years earlier and has been suffering from a "cerebral infarction" for the past 8 years. In addition, he reported not having a family history of malignant disease. Upon physical examination, no palpable lymphadenopathy was found.

A contrast neck CT scan using uniform contrast enhancement showed that the right vocal cord was unevenly thickened, but no discrete mass, cartilage invasion, or lymphadenopathy was detected (Figure 1). On MRI, there was a non-uniform signal of the right vocal cord with ragged edges (Figure 2). Laryngoscopy detected an irregular swelling in the right vocal cord, while the bilateral vocal folds moved symmetrically (Figure 3). Biopsies of the mass showed that the tumor cells were distributed in sheets, with obvious atypia (Figure 4). Immunohistochemically, the cells stained positive for leukocyte common antigen, CD3, CD2, TIA-1, granzyme-B, Bcl-2, CD56, MUM1, CD5, CD7, Bcl-6, Ki-67 (80%), and Epstein-Barr virus-encoded RNA, whereas they were negative for CK, CK5/6, P40, P63, CD4, CD8, CD20, CD79a, CD10, cyclin D1, and CD23. On the basis of the morphology and immunophenotyping results, a diagnosis of NK/T-cell lymphoma was made. Subsequently, a full body PET scan was obtained to evaluate systemic malignancies other than those in the right vocal cord, and the left ilium and multiple vertebrae were also found to be involved (Figure 5).

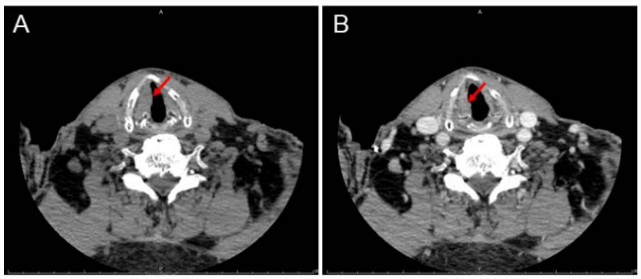

Figure 1: Neck Computed Tomography (CT) image showing the unevenly thickened right vocal cord (red arrows). (A) Plain CT; (B) Contrast-enhanced CT.

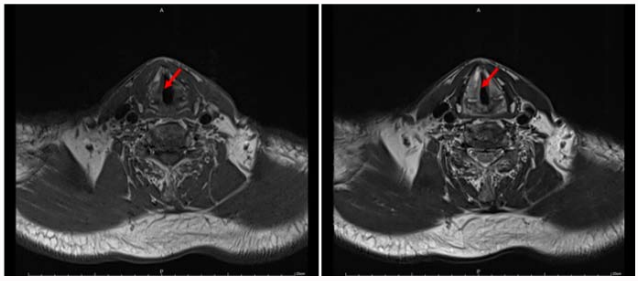

Figure 2: Magnetic resonance imaging of the tumor in the right vocal cord (red arrows). (A) T1-weighted; (B) T2-weighted.

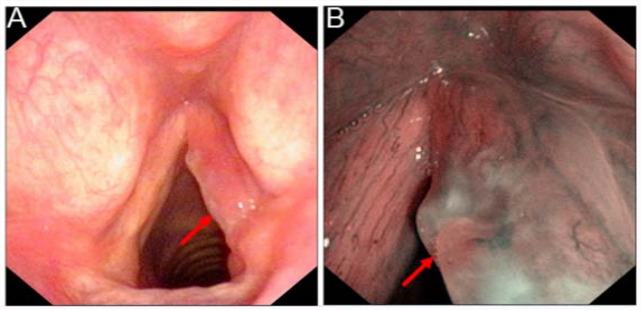

Figure 3: Electronic laryngoscopy image showing an irregular swelling in the right vocal cord (red arrows). (A) White light endoscopy; (B) Narrow-band imaging.

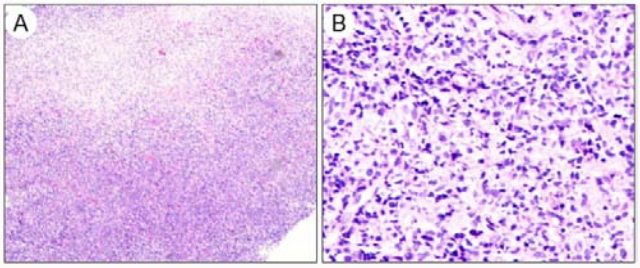

Figure 4: Hematoxylin and eosin staining of tumor sections showing that cells were distributed in sheets, with obvious atypia. Original magnification: (A) x100; (B) x400.

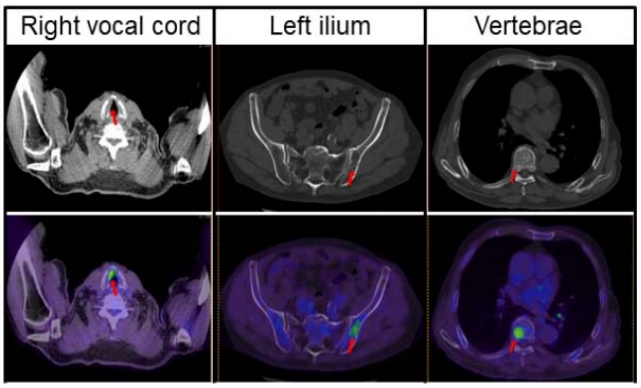

Figure 5: Positron Emission Tomography-Computed Tomography (PET-CT) imaging. PET-CT revealed that the right vocal cord, left ilium, and vertebrae displayed increased fluorodeoxyglucose uptake.

Retrospective study

A total of 62 articles comprising 90 cases were included in this study. The earliest report was published in 1988, while the latest one was published in 2019. The detailed patient information is shown in Table 1. The average patient age was 45 years old, range from 16 to 85 years. Among them, 20 (22.22%) patients were older than 60 years, while 70 (77.78%) patients were younger. There were 63 male patients (70.00%) and 27 female patients (30.00%), with a male-to-female ratio of 7:3. To investigate the association of smoking history with the

Table 1: Clinical features of the primary laryngeal lymphoma in Chinese patients.

Clinical Features	Variables	Number	%
Age			
	≥ 60	20	22.22
	<60	70	77.78
Gender			
	Male	63	70
	Female	27	30
First symptom			
	Hoarseness	51	56.67
	Pharyngalgia	22	24.44
	Foreign body sensation	9	10
	Dysphagia	6	6.67
	Dyspnea	2	2.22
B symptoms			
	Yes	24	26.67
	No	66	73.33
Involvement site			
	Supraglottic	44	48.89
	Supraglottic-glottic	12	13.33
	Glottic	15	16.67
	Glottic-subglottic	2	2.22
	Subglottic	8	8.89
	Transglottic	7	7.78
	NA	2	2.22
Pathological subtype			
	Hodgkin's lymphoma	1	1.11
	B-cell non-Hodgkin's lymphoma	35	38.89
	T-cell non-Hodgkin's lymphoma	16	17.78
	NK/T-cell non-Hodgkin's lymphoma	12	13.33
	NA	26	28.89
Disease course			
	≥1 year	20	22.22
	3 month-1 year	33	36.67
	<3 month	30	33.33
	NA	7	7.78
Tumor morphology			
	Swelling	81	90
	Ulceration	7	7.78
	NA	2	2.22
Treatment			
	Surgery	7	7.78
	Chemotherapy	13	14.44
	Radiotherapy	7	7.78
	Surgery+chemotherapy	4	4.44
	Surgery+radiotherapy	5	5.56
	Chemotherapy+radiotherapy	18	20
	Surgery+chemotherapy+radiotherapy	5	5.56
	NA	31	34.44
Follow up			
	≥1 year	22	24.44
	<1 year	11	12.22
	NA	57	63.33
Outcome			
	Dead	8	8.89
	Alive	32	35.56
	NA	50	55.56

Table 2: The smoking ratio between male and female patients.

		Smoking			
		Yes		No	
Gender	Male	5	62.50%	3	37.50%
	Female	2	40.00%	3	60.00%

incidence of laryngeal lymphoma between male and female patients, their smoking histories, summarized in Table 2, were assessed. More men than women smoked, which correlated with the incidence of laryngeal lymphoma. The average ages of male and female patients were similar: 45 (range from 16 to 85 years) and 44 (range from 18 to 71 years), respectively.

The disease course ranged from 2 days to 6 years. Initial symptoms included hoarseness (51/90, 56.67%), pharyngalgia (22/90, 24.44%), foreign body sensation (9/90, 10%), dysphagia (6/90, 6.67%), and dyspnea (2/90, 2.22%). Furthermore, B symptoms occurred in 24 patients (26.67%).

The involved site could be regarded as the location where the tumor originated. Most cases originated in the supraglottis (44/90, 48.89%). However, in many cases, more than one area was involved, and the initial site was difficult to determine. Regarding tumor morphology, the vast majority of patients presented with a swelling in the larynx (81/90, 90.00%), while only a small fraction of tumors were characterized as ulcerated (7/90, 7.78%). The specific pathological subtype was not provided in 26 cases. For the other cases, all but one of the 64 lymphomas were NHLs. Among them, 35 (38.89%) patients had B-cell-derived NHLs, 16 (17.78%) had T-cell-derived NHLs, and 12 (13.33%) had NK/T-cell-derived NHLs.

Chemotherapy and radiotherapy are the main therapeutic modalities used in the treatment of lymphomas. Thirteen (14.44%) patients received only chemotherapy, seven (7.78%) received only radiotherapy, and 18 (20.00%) received combined therapy. Twenty-one (23.33%) patients first underwent surgery for their laryngeal cancer, and lymphoma was pathologically diagnosed postoperatively. Information about follow-up and outcomes was not provided in many of the published reports. Results on 33 patients, however, were available, and follow-up time ranged from 1 month to 20 years. For 40 patients with outcome data during follow-up, the mortality rate was 20% (8/40).

Discussion

Lymphomas, which usually present with lymphadenopathy, are the malignant proliferation of lymphocytes [7]. Primary lymphoma of the larynx is rare. In this study, we presented an unusual case of a primary laryngeal NK/T-cell lymphoma that was located in the

vocal folds at multiple aspects. Furthermore, we also performed a retrospective analysis on patients with laryngeal lymphoma using studies published in the Chinese language literature and found some unique features that were different from those in other countries. Therefore, our study has added to the data on laryngeal lymphomas and may help in gaining a better understanding of this disease.

The case we presented was that of a 70-year-old man with a primary laryngeal lymphoma. In addition, from our Chinese language literature search, patients with laryngeal lymphoma ranged in age from 16 to 85 years, the mean age was 45, and the male-to-female ratio was 7:3. Another study based on Chinese people showed similar results in that the average age of male and female patients was 46.10 and 42.38 years, respectively, and the male-to-female ratio was 3.1:1 [8]. However, in Kim et al.'s report based on an English language literature search, the mean age of patients was 53.9 ± 18 years, and the male-to-female ratio was 35:22 [9], while in Hong et al. [10] study based on the surveillance, epidemiology, and end results cancer incidence database, the mean age of patients was 64.2 years, and 53% of the patients were males [10]. Besides the limitation of there being a relatively low number of cases in general, the difference in the age and gender of patients from China compared with those of patients from other countries could be attributed to a variety of factors including both genetic and environmental. Our results showed that there were more male than female smokers, which suggested that smoking might act as an important factor in the oncogenesis of laryngeal lymphomas. However, owing to the limited sample size, statistical significance was not reached.

The early symptoms of laryngeal lymphoma are usually indistinguishable. In our study, hoarseness was the most common first symptom, while other initial symptoms included pharyngalgia, foreign body sensation, dysphagia, and dyspnea. Only a few patients had B symptoms. All these symptoms were non-specific, similar with symptoms in other laryngeal tumors. On endoscopy, the majority of tumors appeared as swelled masses, while some appeared as ulcerations. The patient was referred to our hospital because of progressive hoarseness for more than 2 months, and he displayed irregular swelling in his vocal cord. As laryngeal lymphoma has some obvious symptoms like hoarseness and pharyngalgia, most patients seek medical attention early in the disease course. In our study, about one third of patients were diagnosed within 3 months after their first symptoms occurred.

The image performance in laryngeal lymphoma was also non-specific. In previous reports, most cases demonstrated uniform moderate enhancement on CT imaging, were metabolically active on a PET-CT scan, and had a heterogeneous appearance on MRI [11,12]. Laryngeal lymphomas also invade cartilage and muscle, which is similar with squamous cell carcinomas. In our case, the tumor presented as an unevenly thickened vocal cord with uniform contrast enhancement on CT imaging, which was consistent with previous reports. However, no evidence of central necrosis or abnormal calcifications was seen in laryngeal lymphoma, which might help distinguish it from aggressive neoplasms [12]. It was noteworthy that the larynx was not the only malignant site; the left ilium and multiple vertebrae were also involved, as seen on a whole-body PET-CT scan. But if the bone lesion was the primary lesion, localized bone pain should be the first and dominant symptom. Therefore, we considered that the larynx was the primary tumor site.

If neoplastic proliferation of lymphocytes occurs in the larynx, then most primary laryngeal lymphomas are located in the supraglottis, which contains lymphoid tissue [6]. In our analysis of the literature, about half of the cases originated in the area of the supraglottis, which was consistent with the location of the lymphoid tissue. Moreover, in previous reports of primary laryngeal lymphomas, most cases were B-cell-derived NHLs. NK/T-cell lymphomas involving the larynxes are rare [13]. In our study, 38.89% of patients had B-cell-derived NHLs, and 13.33% patients had NK/T-cell-derived NHLs, which was consistent with previous reports. Our case presented with a laryngeal NK/T-cell lymphoma located in the vocal cord, which was unusual and noteworthy.

At present, the treatment of lymphoma is based on an integrated medical approach that combines chemotherapy, radiotherapy, immunotherapy, and surgery [14]. For the treatment of laryngeal lymphomas, chemotherapy and radiotherapy are the most common therapeutic strategies [15]. In our analysis of the literature, most patients accepted at least one of the two strategies, although some patients were treated surgically because of a misdiagnosis. The prognosis of laryngeal lymphoma depends on multiple factors, including an accurate biopsy, the presence of B symptoms, cell type, gender, staging, lymph node involvement, and response to treatment [8-10]. Therefore, individualized therapy should be advocated in the treatment of laryngeal lymphoma.

Our case of a NK/T-cell lymphoma originated in the vocal folds of the larynx and metastasized to the left ilium and vertebrae. The imaging performance was analyzed using CT and MRI, the morphology was evaluated using laryngoscopy, the definitive diagnosis relied on histopathological examination, and metastasis was assessed using whole-body PET-CT scanning. Compared with previous reports, we have provided a more comprehensive and detailed description of a laryngeal lymphoma case, which could help further the understanding of this disease.

In conclusion, laryngeal lymphoma is a type of lymphoma involving the larynx and shares similar characteristics with both lymphomas and laryngeal neoplasms. Laryngeal lymphomas lack the specificity in clinical manifestations and imaging performance, which make them difficult to differentiate from other laryngeal tumors. The definitive diagnosis of laryngeal lymphoma depends on histopathological examination and further typing using immunohistochemistry. Furthermore, PET-CT plays a significant role in assessment of the whole-body condition in patients with laryngeal lymphoma. Therefore, when patients present with laryngeal neoplasms, physicians should consider the possibility of a lymphoma.

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