Int J Clin Exp Pathol 2023;16(5):99-107
www.ijcep.com /ISSN:1936-2625/IJCEP0149160

Case Report

Primary thyroid lymphoma – report of four cases and literature review

Haoying Sun, Jinzhu Ma, Yibo Chen, Ming Liu

Department of Thyroid and Breast Surgery, The Affiliated Hospital of Inner Mongolia Medical University, No. 1 Tongdaobei Street, Huimin District, Hohhot 010050, Inner Mongolia, China

Received January 16, 2023; Accepted May 17, 2023; Epub May 20, 2023; Published May 30, 2023

Abstract: Objective: This study aims to investigate the pathogenesis, clinical characteristics, diagnosis, treatment, and prognosis of primary thyroid lymphoma (PTL) for a better understanding of the disease and a more accurate PTL diagnosis, thereby preventing misdiagnosis and mistreatment. Methods: The clinical manifestations, biochemical examination, ultrasound examination, imaging examination, pathologic examination, diagnosis, and treatment of four PLT patients admitted to the Department of Thyroid and Breast Surgery of the Affiliated Hospital of Inner Mongolia Medical University from January 2010 to December 2020 were retrospectively analyzed. Results: Diffuse large B-cell lymphoma (DLBCL) expressing cluster of differentiation 20 (CD20) were detected in all four PTL patients. Hashimoto's thyroiditis (HT) with increased anti-thyroglobulin antibodies (TGAb) occurred in two PTL patients, while antithyroid peroxidase autoantibody (TPOAb) was increased in three cases. All four patients underwent surgical and chemoradiotherapy treatments. Patients were without tumors during the follow-up ranging from 8 to 55 months. Conclusion: PTL is a primary extranodal lymphoma of the thyroid and is mainly derived from B-cell non-Hodgkin's lymphoma. The pathogenesis of PTL remains unclear, but it is closely related to HT. Clinical diagnosis in this study was determined by either needle biopsy or surgical resection.

Keywords: Thyroid lymphoma, non-Hodgkin's lymphoma, immunohistochemical, diagnosis, differential diagnosis

Introduction

Primary thyroid lymphoma (PTL) is a rare malignant tumor, accounting for 1%-5% of thyroid malignancies and less than 2% of extranodal lymphomas, with an annual incidence of about two million [1]. PTL usually occurs in people between 50 and 80 years old, with a higher male-to-female ratio of 1:0.75. PTL usually develops after the age of 70, but the onset of the disease occurs earlier in men [2]. The lymphoma consists of precursor lymphocyte tumors, mature B-cell tumors, mature NK/T cell tumors, and Hodgkin's lymphoma (HL). Lymphoma of the thyroid gland is mainly non-Hodgkin's lymphoma (NHL) of B-cell origin. Diffuse large B-cell lymphoma (DLBCL) is the dominant histologic subtype in NHL (70%), followed by mucosa-associated lymphoid tissue (MALT) B-cell non-Hodgkin's lymphoma, follicular lymphoma (FL), Mantle lymphoma (ML), Burkitt lymphoma (BL), and angioblastic lymphoma [3]. DLBCL is a more aggressive histologic type, and 60% of patients already have local and distant metastasis at the time of diagnosis, leading to poor prognosis. The expressions of cluster of differentiation 20 (CD20), B-cell lymphoma 6 protein (Bcl-6), B-cell lymphoma 2 protein (Bcl-2), and multiple myeloma oncogene-1 (Mum-1) are usually positive. Additionally, DLBCL can be divided into germinal center B-cell-like (GCB) and non-germinal center B-cell-like (N-GCB). The former is characterized by CD10+, Bcl-6+/-, Mum-1+/- or CD10-, Bcl-6+, Mum-1-, while the latter is characterized by CD10-, Bcl-6+/-, Mum-1+ or CD10-, Bcl-6-, Mum-1-. The level of Ki-67 is usually greater than 40%, and some can exceed 90%. In general, the Ki-67 positive index of MALT is usually less than 30%, while the Ki-67 positive index in DBLCL is more than 30%, and the Ki-67 index in BL is close to 100%. Thus, a high Ki-67 positive index should be considered for high-grade lymphoma.

Table 1. Biochemical data of the four PTL patients before treatment

NO.	Age (Year)	LDH (U/L)[a]	β2-Mg (mg/L)[b]	HT[c]	TGAb (IU/ml)[d]	TPOAb (IU/ml)[e]	Ki-67
A	71	403	2.65	Yes	4000	129	70%+
B	63	132	2.29	Yes	220	7.65	90%+
C	33	159	1.06	No	117	228	80%+
D	53	220	2.35	No	25	15	70%+

Note: a: LDH (lactate dehydrogenase), Normal range (110-240 U/L); b: β2-Mg (β2 microglobulin), Normal range (0.8-2.2 mg/L); c: HT (Hashimoto's thyroiditis); d: Normal range (0-115 IU/ml); e: Normal range (0-34 IU/ml).

Table 2. Biochemical data of the four PTL patients after treatment

NO.	Age (Year)	LDH (U/L)[a]	β2-Mg (mg/L)[b]	TGAb (IU/ml)[c]	TPOAb (IU/ml)[d]
A	71	203	1.23	100	27
B	63	197	1.18	98	18
C	33	148	0.99	75	24
D	53	198	1.78	43	29

Note: a: LDH (lactate dehydrogenase), Normal range (110-240 U/L); b: β2-Mg (β2 microglobulin), Normal range (0.8-2.2 mg/L); c: Normal range (0-115 IU/ml); d: Normal range (0-34 IU/ml).

MALT accounts for most of the remaining 30% of lymphoma cases and can be characterized by lymphocyte colonization of thyroid follicles and immunoglobulin light chains. MALT exhibits positive expressions of BCL2 and CD20 and negative expressions of CD5, CD10, and CD23. MALT is a low-grade indolent tumor and an indication of early-stage lymphoma [4]. In contrast, FL is a rare B-cell-derived tumor with abnormal Bcl-2 expression, accounting for 5% of all PTL, whereas Hodgkin's lymphoma of the thyroid accounts for 1-2% of PTL. T-cell-derived thyroid lymphoma is rarer and has a worse prognosis than B-cell lymphoma [4].

The etiology, pathogenesis, clinical manifestations, diagnosis, and treatment of PTL are not well understood. In this regard, there are only four reported cases of PTL in the Affiliated Hospital of Inner Mongolia Medical University over the past 10 years. Herein, we reviewed the relevant PTL studies, evaluated the existing cases, and conducted genetic testing for newly discovered PTL cases for a better understanding of PTL. The three databases of Pubmed, CNKI, and Wanfang were searched, and English was the only foreign language used. The keywords searched were "thyroid lymphoma", "non-Hodgkin's lymphoma", "immunohistochemical", "diagnosis", and "differential diagnosis". Data were retrieved from January 2000 to November 2021 and restricted to both the title and abstract.

Case report

General conditions

The study was approved by the Ethical Committee of the Affiliated Hospital of Inner Mongolia Medical University. The Affiliated Hospital of Inner Mongolia Medical University is the largest clinical and teaching center in Inner Mongolia, with an average of 2000 thyroid surgeries per year, including 600 cases of thyroid cancer per year. However, only four PTL cases were reported over the last 10 years, leading to a large age gap.

From 2010 to 2020, the Department of Thyroid and Breast Surgery in the Affiliated Hospital of Inner Mongolia Medical University reportedly admitted over 4000 cases of malignant thyroid tumors, among which four cases (1%) were PTL-related. There were two males and two females with an average age of 55(±14.21) years old. In all four cases, the thyroid gland was enlarged and hard. One case was accompanied by hoarseness, and three cases were accompanied by neck distention and choking sensation. One patient developed fatigue, night sweats, and fever.

Laboratory examination

One case reported elevated lactate dehydrogenase (LDH). Three cases reported elevated β2 microglobulin (β2-Mg). Three cases reported elevated TGAb, and two cases reported elevated TPOAb (**Table 1**). Bone marrow biopsy was performed in all four cases, and the results indicated normal proportion and morphology of granulocytes, lymphocytes, and monocytes. The laboratory tests of the patients after treatment are displayed in **Table 2**. The biochemical indices of the four PTL patients were within the normal range, and thyroid function was reported to be recovered.

Imaging examination

A neck color ultrasound examination was performed and reported irregular hypoechoic nod-

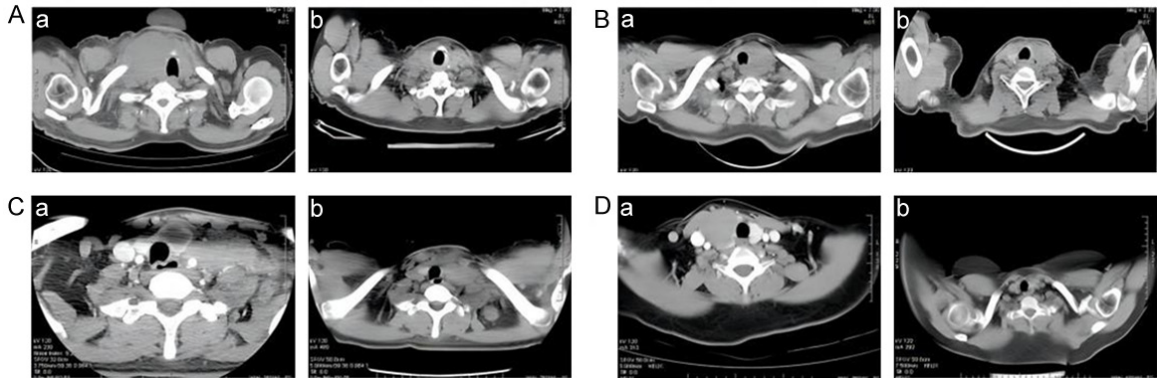

Figure 1. Aa: The thyroid gland is enlarged, with the right lobe protruding downward into the mediastinal sternum, and the trachea is compressed and shifted to the left. Ab: The thyroid gland is significantly reduced, and no enlarged mediastinal lymph nodes are observed. Ba: The left lobe of the thyroid gland increases in volume and decreases in internal density. Bb: The left lobe of thyroid is absent. The morphological structure and signal of the right lobe of thyroid are normal. Ca: Inhomogeneous punctate high density calcification shadow is observed in the low-density lesion, linear high density shadow is identified at the edge, and the trachea is tilted to the right. Cb: After thyroid surgery, the mediastinum is centered, and no abnormally enlarged lymph nodes are observed. Da: The right lobe of the thyroid increases in volume and decreases in density. The trachea is centered without compression or displacement. The thyroid gland is clearly demarcated from surrounding structures. Db: After the resection of the right lobe of the thyroid gland, the mediastinum is in the middle, and there is no swollen lymph node shadow in it.

ules in the thyroid gland with poorly defined boundaries and a small amount of blood flow. A neck or chest CT examination was also performed (**Figure 1**). The Philips Brilliance 64-slice spiral CT was used, and the parameters were set accordingly for each patient. The scanning tube voltage was 120 kV, the current was 250 mA, the layer thickness was 5 mm, and the spacing was 5 mm. **Figure 1Aa** displays the enlargement of the right lobe of the thyroid and the displacement of the trachea to the left under pressure in patient A before treatment. **Figure 1Ab** displays the normal size and density of the thyroid gland, a centered trachea, and no enlarged lymph nodes in the mediastinum after treatment. **Figure 1Ba** indicates the increased volume and the decreased internal density of the left thyroid lobe of patient B before treatment. **Figure 1Bb** displays the absence of the left thyroid lobe after treatment, without any abnormalities in the morphological structure and signal of the right lobe or enlarged lymph nodes in the neck. **Figure 1Ca** features patient C before treatment, where an obvious mass shadow was identified in the left lobe of the thyroid gland. The shadow was more intense at the edges, and multiple enlarged lymph nodes were detected in the neck. **Figure 1Cb** presents the absence of the left lobe of the thyroid gland, with no obvious abnormalities in the right lobe and no enlarged lymph nodes in the neck after treatment. **Figure 1Da** displays the increased volume and decreased density of the right lobe of the thyroid gland in patient D before treatment. A low-density shadow was also observed. **Figure 1Db** presents the absence of the right thyroid lobe after treatment. The volume and size of the left lobe were not significantly abnormal.

Histopathologic examination and diagnosis

The tumor was fixed in a 10% neutral formaldehyde solution and was then sampled, embedded in paraffin, and sectioned at 5-7 microns. Tissue sections were stained with hematoxylin and eosin, dehydrated until transparent, and observed under a light microscope. For immunohistochemical staining, 5-micron sections of formalin-fixed paraffin-embedded tissue were placed on positively charged slides and dried. After paraffin removal, endogenous peroxidase activity was quenched with hydrogen peroxide in methanol, and the sections were then hydrated with water. EnVision two-step method was used, and the primary antibodies included CD20 and Bcl-6. The images were collected and analyzed from observation under a microscope (10*40). The above-mentioned antibody, immunohistochemistry high sensitivity kit, and DAB color development kit were purchased from DAKO.

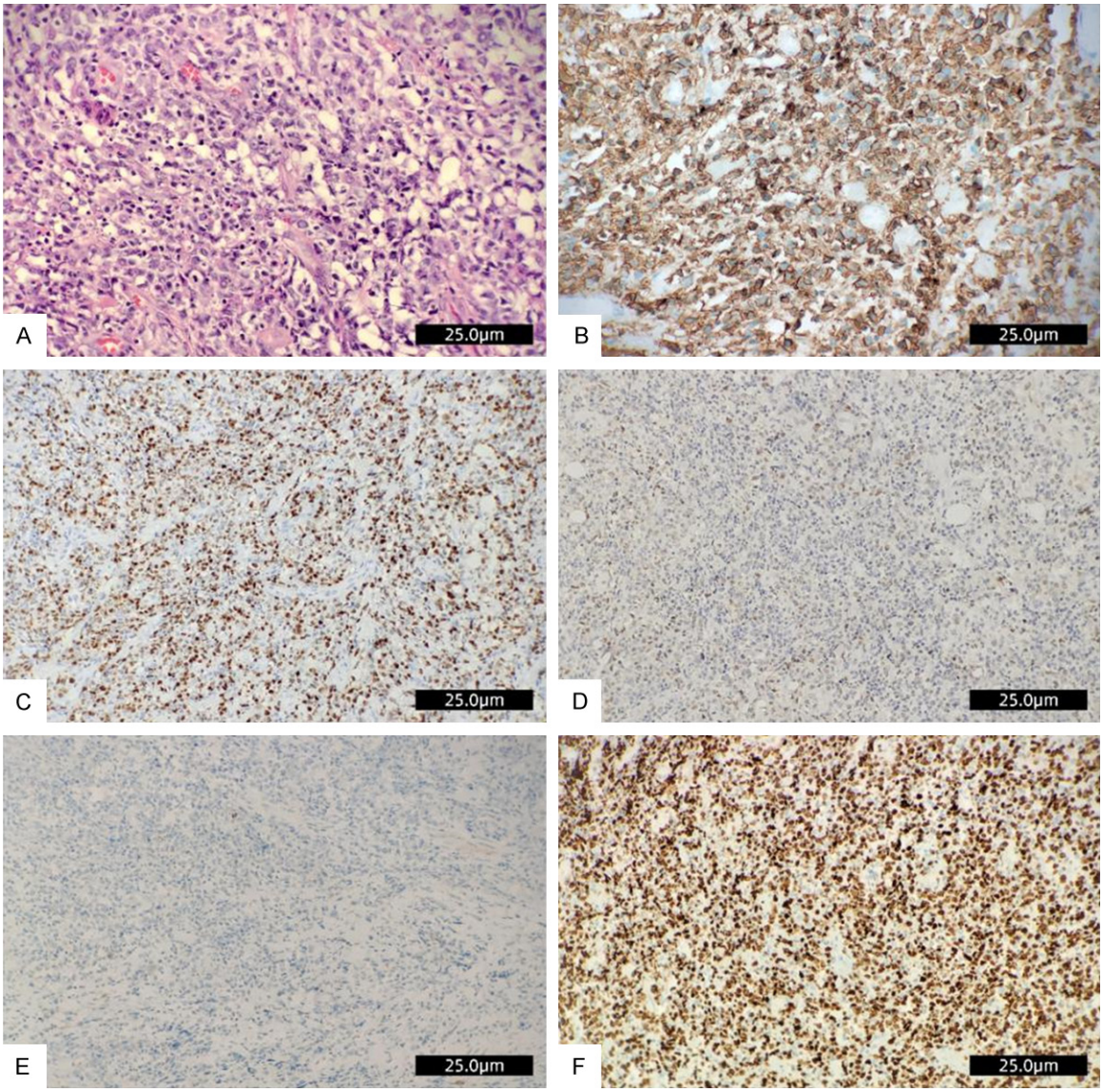

Figure 2. A: H&E staining (10*40), medium or large cells, round or oval, with nucleoli and mitotic images, residual follicular epithelium, diffuse patellar distribution. B: CD20 positive (10*40). C: Bcl-6 positive (10*40). D: Mum-1 positive (10*40). E: CD10 negative (10*40). F: Ki-67 is about 90%+ (10*40).

The pathologic diagnosis of the four PTL patients was N-GCB (**Figure 2A**: H&E staining, 10*40). CD20 (**Figure 2B**, 10*40), Bcl-6 (**Figure 2C**, 10*40), and Mum-1 (**Figure 2D**, 10*40) were positive, while CD10 (**Figure 2E**, 10*40) was negative. Ki-67 (**Figure 2F**, 10*40) was about 90%+.

Treatment and follow-up

Among the four patients, three had surgical resection and one had ultrasound-guided needle biopsy. Two of the patients had the complication of HT. Three patients were in Stage II Group A, and one patient was in Stage IV Group A. All four patients were treated with chemotherapy after diagnosis of lymphoma. The chemotherapy regimen was CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone) or R-CHOP (rituximab+CHOP) for 6-8 cycles, and one patient received regional chemoradiotherapy. The biochemical indexes of the four cases of thyroid lymphoma after treatment are displayed in **Table 2**. All patients were followed up by telephone for 8-55 months until October 2021. All patients reported tumor-free survival.

Discussion

Pathogenesis

Thus far, the pathogenesis of PTL is not fully clarified. Normal thyroid tissue does not contain lymphoid tissue, and the appearance of lymphocytes promotes the formation of PTL. MALT PTL tissue types are more inert, and patients have better disease progression and prognosis. In contrast, DLBCL has stronger invasiveness and a poor prognosis. Yang et al. reported that DLBCL could be transformed from existing MALT [5]. Sharma et al. found that thyroid autoimmunity was more common in MALT lymphomas than in other subtypes. This could be related to the routine use of flow cytometry for diagnosis, which is consistent with the previous hypothesis that chronic antigenic stimulation of marginal cells leads to slow malignant transformation [6]. However, due to the small number of cases in this study, all PTL types were common DLBCL. In a larger-scale PTL report, 154 of 171 adult patients (90%) were diagnosed with HT within 1-362 months before PTL diagnosis [7]. Antonio et al. reported that HT was the most important risk factor for PTL, and increased the risk of PTL by 40-80 times [8]. MALT can occur in inflammatory lymphatic tissues, including HT [9]. In addition, genetic sequence analysis of PTL tissues obtained from HT patients revealed the presence of homologous clonal bands in HT and PTL tissues [10]. Other studies reported PTL and HT as two independent diseases, and there was no HT in PTL patients. Hence, it was unclear whether HT was necessary for the progression of PTL [11].

Molecular factors

In recent years, many proteins associated with malignant tumors have been discovered by immunohistochemistry. These proteins are considered possible biomarkers for early detection and therapeutic targets of diseases. The Wnt signaling pathway is one of them, and its maladjustment is related to the formation of malignant tumors. A recent study demonstrated that the Wnt5a protein and its receptor Ror2 are related to the pathogenesis and progression of PTL [12]. However, this was based only on a clinical study with a sample size of 22 cases, so the association between PTL and Wnt5a/Ror2 requires further support. Notably, Ror2 is not expressed in other hematologic malignancies but is increased in normal thyroid tissues. Therefore, further research is required to evaluate the correlation between Wnt5a/Ror2 and PTL.

Clinical manifestations

The clinical manifestations of PTL include the rapid growth of neck masses or thyroid masses in a short period. The initial clinical presentation of two PTL cases was a rapidly growing goiter [13]. This was the same as the clinical manifestations of the four PTL patients in this study. Patients with large masses may have compression symptoms: dysphagia, dyspnea, and hoarseness. Typical symptoms of Horner syndrome, superior vena cava syndrome, and B-cell lymphoma, such as fever, night sweats, and weight loss, are relatively rare [14]. Thyroid masses on palpation are often hard and well-defined. DLBCL is more aggressive than MALT and follicular lymphoma. In comparison, the age of onset in this study was younger, and this was related to the small sample size.

Imaging examination

Ultrasonography has become a routine examination for differentiating benign and malignant thyroid nodules. PTL tumor cells have uniform and dense growth, few interstitial components, and good acoustic permeability, which makes the capsule edge of the thyroid tumor clearer and the echo behind the gland more enhanced [15, 16]. Mixed ultrasound imaging reported diversity with significant hypoechoic signal inside the thyroid gland and an enhanced posterior echo, which distinguishes PTL from thyroid cancer, subacute thyroiditis, and benign thyroid tumor [17]. However, ultrasonography has some limitations in evaluating the malignancy of thyroid disease, especially in the retropharyngeal space, mediastinum, adjacent organs, and lymph nodes. The nodular type of all four cases in this study was hypoechoic without microcalcification or cystic changes, which was consistent with earlier findings.

CT has excellent sensitivity and specificity for the clinical staging of DLBCL and extranodal metastasis. Some researchers have classified the CT manifestations of PTL into three types: single nodular type, multiple nodular types, and

diffuse large swelling type [18]. A CT scan of PTL is usually isodensity or slightly lower density, with homogeneous parenchymal density and rare calcification and cyst or necrotic foci. The main feature of the lesion after enhancement is that the edge of the tumor has a line-like enhancement, which is a specific manifestation of PTL. In addition, CT plays an important role in monitoring and evaluating the therapeutic effect of chemotherapy and timely detection of chemotherapy resistance. CT can display the overall picture of the tumor with the lesion range and surrounding tissues to complement the ultrasound image.

On the contrary, MRI has no obvious comparable advantages over CT, and it is mainly used for planning in radiotherapy. Fluorodeoxyglucose positron emission tomography (FDG-PET) is often used for post-treatment review to evaluate the therapeutic effect of the treatment and tumor recurrence [19].

Biochemical examination

The elevated levels of serum anti-TGAb and TPOAb in some PTL patients suggested a correlation between PTL and HT, which may help with the clinical diagnosis of PTL. Travaglino et al. reported that 78.9% of PTL patients also had HT, 65.3% of PTL patients had elevated levels of TGAb and TPOAb, and 64% of PTL patients were confirmed to have had HT [20]. This finding is consistent with the four cases in this study. Serum LDH and β2-Mg are mainly synthesized by the lymphatic system and are elevated in response to the dysregulation of tumor genes and increased lymphocyte proliferation rate. Hence, these can be used as prognostic indicators for lymphoma. Additionally, β2-Mg can also be used to monitor tumor recurrence [21].

Pathological examination

The final diagnosis of PTL is a combination of fine-needle aspiration (FNA), core-needle aspiration (CNB), and surgical excision biopsy.

DLBCL, with a large number of high-density monotonic atypical cells, is easier to diagnose, while MALT, with a diverse microscopic appearance, is usually difficult to distinguish from thyroiditis. In recent years, the emergence and development of FNA combined with flow cytometry and immunohistochemical staining technology have increased the diagnostic value of FNA [22]. For some PTL patients, the expressions of CDC25A and CDC25B with carcinogenic potential had increased, which subsequently increased in sensitivity and specificity to FNA. However, the role of FNA in the diagnosis of PTL is still challenged by the lack of samples and integrity. PTL is also difficult to distinguish from autoimmune inflammation due to their strong similarities histologically and pathologically.

CNB can better maintain the original tissue structure than FNA and obtain more focal tissues, which can improve the accuracy of lymphoma diagnosis from 82% (FNA) to 93% (CNB) [23]. The main postoperative complications of CNB are local pain and discomfort, and the incidence rate of postoperative bleeding is only 1% [24]. Ultrasound guidance can minimize the risk of trauma to surrounding tissues. However, CNB cannot provide a complete sampling of lymph nodes and the relative risks, so it cannot replace surgical biopsy for the diagnosis of PTL.

Thus far, there are no large-scale clinical studies on FNA, CNB, and surgical biopsy on PTL. Additionally, there are no clear indications that a puncture is necessary, and the method of puncture and timing of surgical biopsy are unclear. Therefore, a surgical biopsy should be performed quickly when the diagnosis and typing are not clear.

Differential diagnosis

HT increases the risk of PTL, highlighting the importance of HT diagnosis and the relationship between HT and PTL. The diagnosis of HT is based on clinical symptoms, THAb and TPOAb, ultrasonic characteristics, and pathologic examination. The clinical symptoms of HT are various systemic manifestations caused by goiter and hypothyroidism. Moreover, THAb and TPOAb levels are increased, and the echo of thyroid parenchyma is absent under ultrasound, which is similar to the echo of surrounding muscle tissue. The typical pathologic feature of HT is impaired lymphocyte infiltration, which differentiates into true lymphoid follicles [25]. MALT patients were significantly more prone to HT than DLBCL patients, which indicated the etiological difference between DLBCL and MALT patients.

Anaplastic thyroid cancer (ATC) accounts for 1-2% of the incidence of thyroid malignancies and has similar clinical manifestations to PTL with a rapidly growing large mass, more often seen in elderly patients. However, ATC has different treatment methods and prognoses than PTL. Differential diagnosis is therefore required to distinguish ATC from PTL. ATC develops rapidly and often invades surrounding organs and metastasizes. The average survival rate of ATC is only 6-7 months. ATC presents a huge mass that is accompanied by necrosis, hemorrhage, and calcification, while the structure of PTL is more uniform. Calcification and necrosis are rare in ATC patients [26].

Treatment and prognosis

Researchers have indicated that a combination of surgery and chemotherapy can benefit patients more than surgery alone. The treatment of PTL patients in the Affiliated Hospital of Inner Mongolia Medical University is mainly surgery or puncture pathological diagnosis after chemotherapy and radiotherapy. For stage I E patients, surgery alone, radiotherapy alone, or surgery combined with radiotherapy can be used to treat PTL. For patients with invasive tumor or stage II E and above, radiotherapy combined with chemotherapy is used [27].

Because of the characteristics of lymphoma, surgery is mainly used to obtain a complete tissue biopsy, relieve symptoms of tracheal compression and other complications, or as part of a combined treatment. It is difficult to cure by surgery alone, and often relapses. However, for MALT and the other indolent lymphomas, especially those in I E, only surgical resection can be performed, but a close follow-up examination is required.

Currently, the accepted chemotherapy regimen is CHOP and R-CHOP [28]. For PTL patients at stage I E or II E, radiotherapy is the preferred treatment [29]. Radiotherapy involves field radiotherapy (including thyroid and cervical lymph nodes) and extended field radiotherapy (including involved field and superior mediastinal lymph nodes). For PTL with strong aggressiveness, local invasion, distant metastasis, combined radiotherapy, and chemotherapy should be selected. Graffle-Baker et al. reported that the five-year survival rates of 1408 PTL patients were: I E 86%, II E 81%, III E or IV E 64% [30]. DLBCL had a high degree of malignancies and a relatively low five-year survival rate of 75%, while MALT, FL, and small-cell lymphoma reported five-year survival rates of 96%, 87%, and 86%, respectively.

Conclusion

The Affiliated Hospital of Inner Mongolia Medical University is located in North China, which is an ethnic minority area with Mongolian as the main body. Only four PTL cases were reported over the past 10 years, and there were no reports of PTL in this area before that. This study summarized and analyzed the four PTL cases, reviewed earlier reports, and summarized the pathogenesis, clinical manifestations, diagnosis, and treatment of PTL. However, this study had some shortcomings. The number of PTL patients was small, and the timespan was long. At present, the pathogenesis of PTL is not clear, and chronic antigen stimulation of HT may play an important role in the pathogenesis of PTL. PTL usually occurs in elderly women, and the chief complaint is usually a rapid enlargement of a neck mass in a short time that is accompanied by hoarseness, dyspnea, and other symptoms. Ultrasound and CT examination can differentiate between benign and malignant thyroid tumors. For patients suspected with PTL, ultrasound-guided thyroid puncture biopsy and surgical biopsy should be performed as soon as possible for pathological and immunohistochemical examination. Surgical therapy was used only for the treatment of complications associated with early-stage MALT malignancies that require treatment. For late-stage PTL (i.e., strong invasion, severe local invasion, and distant metastasis), combined radiotherapy and chemotherapy should be used. Although PTL has a good prognosis, it often recurs after several years and requires long-term follow-up.

Disclosure of conflict of interest

None.

Address correspondence to: Ming Liu, Department of Thyroid and Breast Surgery, The Affiliated Hospital of Inner Mongolia Medical University, No. 1 Tongdaobei Street, Huimin District, Hohhot 010050, Inner Mongolia, China. E-mail: liumingfy@163.com

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