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Pathological Features of Primary Thyroid Lymphoma

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Abstract

A primary thyroid lymphoma is a type of malignancy that originates in the thyroid gland. Most are either a Diffuse Large B-Cell Lymphoma (DLBCL) or Mucosa-Associated Lymphoid Tissue (MALT) lymphoma, while some cases develop from a MALT lymphoma. Since the histological features of a primary thyroid lymphoma including rare subtypes are the same as those of a malignant lymphoma arising from sites other than the thyroid, diagnosis is generally not difficult. In contrast, Hashimoto's thyroiditis occurs in the thyroid and more than half of primary thyroid lymphoma and MALT lymphoma cases are associated with that, making it sometimes difficult to distinguish differences for correct diagnosis. This article describes various pathological features of primary thyroid lymphoma including rare subtypes, with the aim of correct pathological diagnosis for affected patients.

Keywords: Thyroid; Diffuse large B-cell lymphoma; Immunohistochemistry

Abbreviations

DLBCL: Diffuse Large B-Cell Lymphoma; MALT: Mucosa-Associated Lymphoid Tissue; PET-CT: Positron Emission Tomography-Computed Tomography; FNA: Fine Needle Aspiration; FNB: Fine Needle Biopsy; LEL: Lymphoepithelial Lesion

Introduction

A primary thyroid lymphoma is a malignant lymphoma originates in the thyroid gland [1]. The term 'primary' designates patients with lymphomatous involvement of the thyroid at the time of diagnosis, with either localized disease or dissemination to nodal or extranodal sites. Most primary thyroid lymphomas are non-Hodgkin type and have a B-cell phenotype that indicates a Diffuse Large B-Cell Lymphoma (DLBCL) [2]. Some DLBCLs constitute large cells transformed from a Mucosa-Associated Lymphoid Tissue (MALT) lymphoma. Since the histological features of a primary thyroid lymphoma including rare subtypes are the same as those of a malignant lymphoma arising from sites other than the thyroid, diagnosis is generally not difficult. In contrast, Hashimoto's thyroiditis occurs in the thyroid, and the distinction between that and a malignant lymphoma composed of small cells is sometimes difficult, as affected patients demonstrate florid lymphoid hyperplasia [2,3]. In addition, other rare types of malignant lymphoma occur in the thyroid, such as T-cell lymphoma [4,5], follicular lymphoma [6], Burkitt lymphoma [7,8] and classic Hodgkin lymphoma [9].

The histological characteristics of a primary thyroid lymphoma vary and it is occasionally difficult to make a pathological diagnosis of cases with a rare subtype. Therefore, for better understanding of distinctive characteristics, the present study was conducted to describe histological features of various primary thyroid lymphoma types.

Epidemiology

A primary lymphoma of the thyroid is rare, and accounts for approximately 5% of all thyroid malignancies and 2% of extranodal lymphoma cases. The female-to-male ratio is 3:1 and mean patient age at time of presentation has been reported to be 65 years [10].

Etiology

Thyroid lymphoma cases are always associated with chronic lymphocytic thyroiditis (Hashimoto's thyroiditis) [11]. And those patients have a significantly increased risk of developing a thyroid lymphoma. For example, the risk among Japanese patients with chronic lymphocytic thyroiditis was found to be 80 times greater as compared to general Japanese population [12].

General Features

Most cases of primary thyroid lymphoma are seen in middle-aged or elderly patients, with the

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most common age at presentation in the 60s [13]. Typical clinical presentation features include rapid thyroid growth, fever, dyspnea, hoarseness, and dysphagia [14]. While the duration of symptoms is usually short as expected, symptom occurrence is more common in patient with tumors exhibiting extrathyroidal extension [15].

Imaging

Ultrasonography findings of the cervix show an asymmetric hypoechoic mass similar to a pseudocyst or characteristic hypoechoic mass invading adjacent non-neoplastic thyroidal tissue, which has the appearance of a towering thundercloud [16]. In addition, features revealed with that imaging modality show an enhanced posterior echo and linear echogenic strand, and lack of calcification. Color Doppler imaging demonstrates a rich blood flow pattern on the hypoechoic mass. In Computed Tomography (CT) findings, a primary thyroid lymphoma shows a low density area, while magnetic resonance imaging indicates a low signal area in both T1 and T2 images.

Macroscopic Appearance

The macroscopic presentation is a solid mass with a homogenous bulging white surface featuring a fish-flesh appearance, which is generally associated with lymphomas. The interface between the tumor and an adjacent gland is usually ill-defined, and shows encapsulation. Large peripherally located lesions tend to invade the thyroid capsule and extend into surrounding soft tissue. Necrosis and hemorrhage are uncommon [2].

Microscopic Features

As for histological types of primary thyroid lymphoma, non-Hodgkin type with a B-cell phenotype accounts for 65% to 85% and MALT lymphoma for 15% to 40% [2]. The histological features of a primary thyroid lymphoma including the histological features of each subclass are the same as those for a malignant lymphoma arising from sites other than the thyroid.

A lymphomatous focus and/or infiltration can be seen adjacent to a lymphoma tumor, with 60% to 70% of patients with a primary thyroid lymphoma positive for antithyroid antibodies at the time of onset, including those who do not have symptoms of Hashimoto's thyroiditis [13].

A DLBCLs shows total architectural effacement by diffuse proliferation of medium or large lymphoid cells, and is composed of large lymphoid cells with centroblastic-like, immunoblastic, or plasmacytoid features. The neoplastic cells show large vesicular nuclei, prominent nucleoli, and a fair amount of cytoplasm [6,10].

On the other hand, MALT lymphoma consists of predominantly small lymphoid cells with variable proportions of centrocyte-like cells, lymphoplasmacytoid lymphocytes, monocytoid B-cells, and interspersed large, transformed lymphocytes [17]. Some cases with MALT lymphoma transform into DLBCL, while others maybe de novo DLBCL [10]. We experienced a case of MALT lymphoma that developed into a diffuse large B-cell lymphoma, and we present details later in this report.

Other rare types include T-cell lymphoma [4,5], follicular lymphoma [6], Burkitt lymphoma [7,8], and Hodgkin lymphoma [9]. The clinicopathological features of these rare subtypes of primary thyroid lymphoma are summarized following.

Immunohistochemistry

Immunohistochemistry findings show that the tumor cells are consistently positive for CD45. In keeping with the B-cell derivation found in nearly all cases, they also exhibit immunoreactivity for pan-B-cell markers, such as CD20. In contrast, CD10 is negative and CD5 is rarely co-expressed with pan-B-cell markers. As seen in a MALT lymphoma component, staining for CD21 and CD35 shows a distorted meshwork of follicular dendric cells corresponding to reactive follicles colonized by the neoplastic lymphocyte. Immunoglobulin (Ig) super family Receptor Translocation-Associated 1 (IRTA-1) is also demonstrated [18].

Genetic Profile

Thyroid lymphomas often exhibit common homologous germline VH genes associated with antithyroid antibodies, further implicating derivation form chronic lymphocytic thyroiditis [19].

A t(3;14) (p14;q32) translocation with FOXP-ICH fusion is seen in about half of all thyroid MALT lymphoma cases, whereas other chromosomal translocations characteristic of this type of lymphoma in other locations are rarely found [20]. DLBCLs show genetic features similar to those of their nodal and other extranodal counterparts, with some cases exhibiting translocation involving BCL6 or MYC, with a 17p11 location.

Primary Thyroid T-Cell Lymphoma

Cases with a T-cell lymphoma originating in the thyroid are extremely rare, with less than 20 reported in English literature. In those, the male/female ratio was 8/12 and median age at presentation was 60.2 years (range, 15 to 86 years), with most patients showing a past history of Hashimoto's thyroiditis [5]. A definitive diagnosis depends on histological and immunohistochemical examination findings, while new techniques, such as flow cytometry and gene rearrangement studies, have enhanced diagnostic efficacy [5].

Follicular Lymphoma

In reported cases of follicular lymphoma, the ratio of females to males is 4.5:1, while ages range from 26 to 72 years (median, 50 years) [6]. Affected patients are typically presented with a single nodular or multinodular mass in the thyroid gland [6]. Some patients with follicular lymphoma have serological and/or clinical evidence of pre-existing auto-immune thyroiditis. Histological features are an extensive and dense lymphoid infiltrate comprised of numerous lymphoid follicles amongst a variably prominent interfollicular density of diffuse components, which effaces the thyroid parenchyma. The lymphoid follicles are absent polarization, show attenuation of mantle zones, and lack tangible body macrophages. The germinal center contains characteristic centrocytes and centroblasts in variable proportions [6]. As for genetic and immunohistochemical features, t(14;18)/IGH-BCL2 and/or Bcl-2 are expressed, and mostly CD10 positive. Good understanding of the spectrum of morphological, immunophenotypic, and genetic characteristics of a follicular lymphoma presented in the thyroid gland will aid both diagnosis and clinical management [6].

Hodgkin Lymphoma

To the best of our knowledge, 17 cases of Hodgkin lymphoma of the thyroid have been reported, with patient age ranging from 18 to 65 years and female predominance [1,9]. The initial presentation tends to occur at a younger age than that in thyroid non-Hodgkin lymphoma patients, and findings commonly show a rapidly enlarging thyroid gland and thyroid mass. Although examination of a biopsy

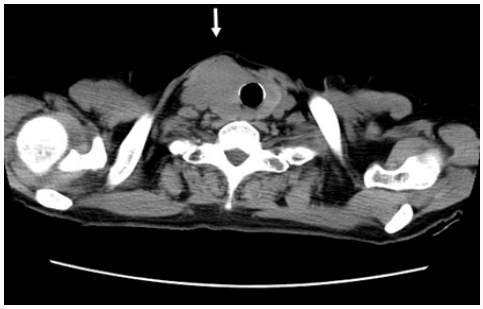

Figure 1: Computed tomography results before initial operation.
Some low-density areas in the right lobe of the thyroid and a 3-cm nodule projecting into the anterior area (arrow) were noted.

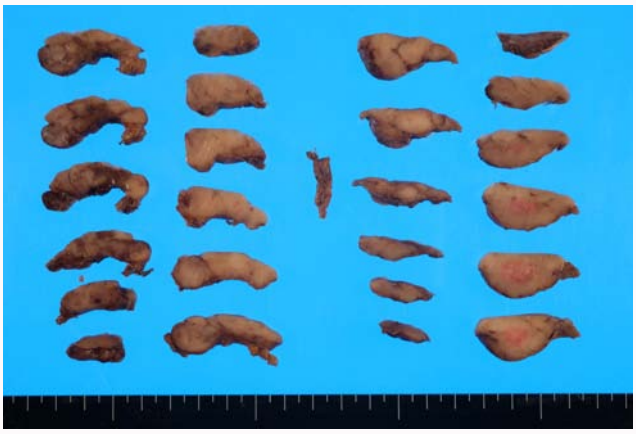

Figure 2: Macroscopic appearance of resected specimen obtained during initial operation.
A well-circumscribed gray-whitish nodule of right lobe of the thyroid.

specimen will usually be necessary to confirm a diagnosis of Hodgkin lymphoma, when adequate material from Fine Needle Aspiration (FNA) can be obtained, that may be valuable for revealing the possibility of such a diagnosis and thereby help to guide subsequent clinical intervention [9].

Thyroid Burkitt's Lymphoma

Primary thyroid Burkitt's lymphoma is a rare and highly aggressive form found in 1% to 2% of thyroid lymphoma cases [7,8]. Our search revealed only 44 related papers published in English literature [8]. The Epstein-Barr virus is associated with Burkitt's lymphoma, and the neoplasm is characterized by intermediate-sized lymphoid cells with a 'starry sky' appearance, which exhibit chromosomal translocations that activate the MYC oncogene [21].

Prognosis and Predictive Factors

Patients with a localized thyroid lymphoma have a favorable prognosis, with a median overall survival of 9.3 years and 5-year disease-specific survival rate of 79%. Lymphoma type also influences survival, with a 5-year disease-specific survival rate of 89% to 100% for MALT lymphoma, as compared to 75% for DLBCL [22].

Poor prognostic indicators include poor performance status, high grade, bulky tumor, advanced patient age, extra capsular extension, and vascular invasion, the same as for a malignant lymphoma of a primary lymph node [23].

Case: Diffuse Large B-cell Lymphoma arising from Mucosa-Associated Lymphoid Tissue Lymphoma

The patient was a 71-year-old female who consulted with an otolaryngologist at our hospital because of swelling from a cervical lesion. CT findings revealed an area of low density in the right lobe of the thyroid and a 3-cm nodule projecting into the anterior area (Figure 1). Chest X-ray, abdominal ultrasonography, and abdominopelvic CT results were normal.

Accumulations in the right lobe of the thyroid and lymph node (right level III, left level II) were revealed by Positron Emission Tomography (PET)-CT. Although FNA smear findings showed only follicular epithelium fragments, Fine Needle Biopsy (FNB) results indicated that small- and medium-sized atypical lymphocytes occupied the obtained specimen. Along with these atypical lymphocytes, a Lymphoepithelial Lesion (LEL) and lymph follicles were observed, along with monotonous proliferation as well as numerous plasmacytoid cells. The results suggested plasma cell neoplasm, though a definitive diagnosis was not obtained. Together, the results led to suspicion of a malignant tumor of the thyroid and the patient underwent a right partial thyroidectomy with regional lymph node dissection.

Pathological features of the resected specimen showed a well-

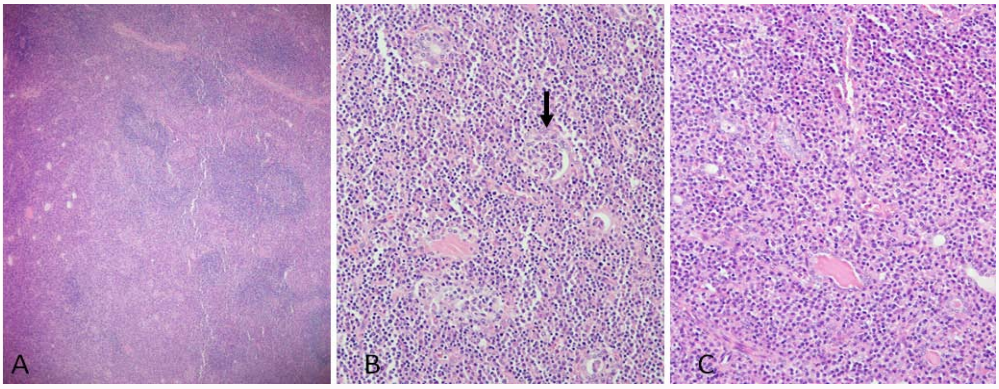

Figure 3: Microscopic features of resected specimen obtained during initial operation.
A. Small-to medium-sized atypical lymphocytes were noted occupying the entire resected specimen along with formation of lymph follicles.
B. Atypical lymphocytes showing monotonous proliferation and lymphoepithelial lesion (arrow).
C. Proliferation of plasmacytoid cells.

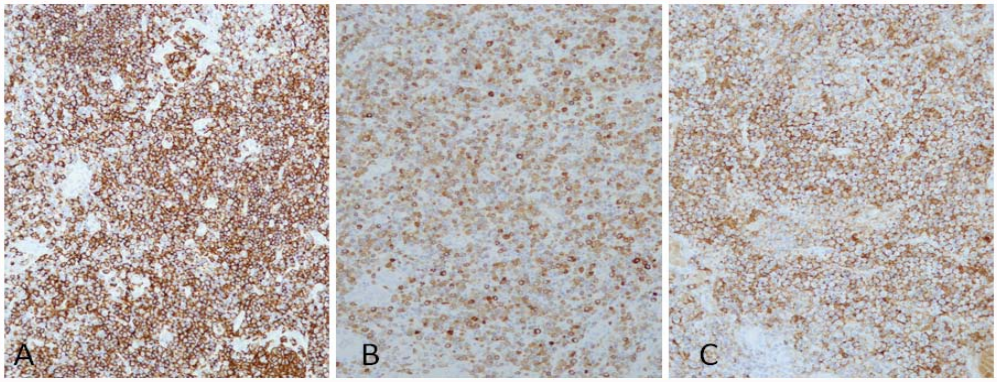

Figure 4: Immunohistochemical features of resected specimen obtained during initial operation. (A) CD20, (B) CD79α, (C) CD138.

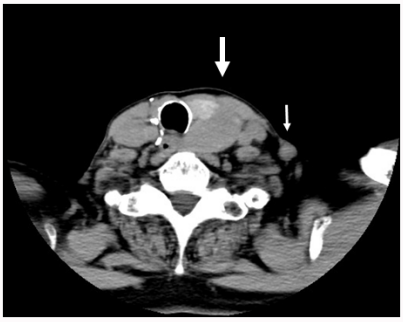

Figure 5: Computed tomography findings prior to second operation.
Enlargement of left lobe of the thyroid was noted (arrow).
Swelling of left cervical lymph node was noted (small arrow).

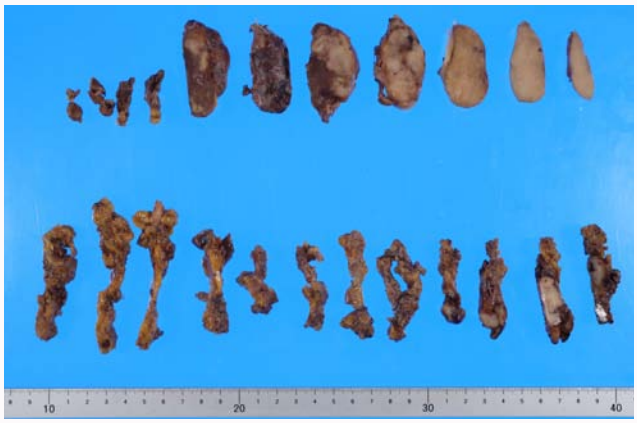

Figure 6: Macroscopic appearance of resected specimen obtained during second operation.
Cut surface showing a heterogeneous white-grayish nodule.

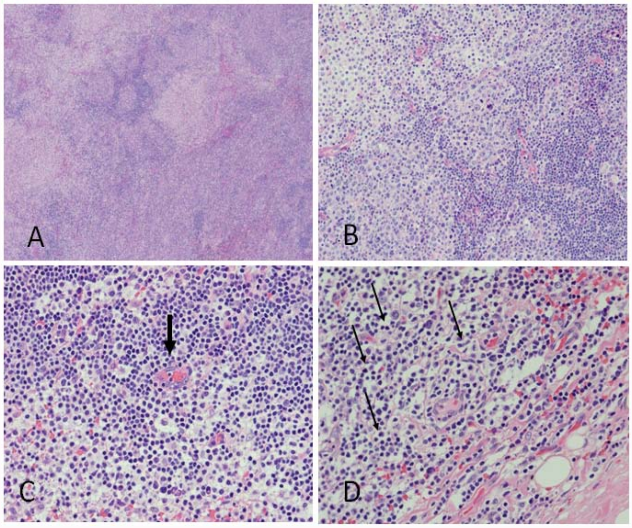

Figure 7: Microscopic appearance of resected specimen obtained during second operation.
A. Residual thyroid occupied by neoplastic cells with lymph follicles including germinal center.
B. Nodular proliferation of large atypical lymphoid cells containing mitotic figures and surrounded by small-to medium-sized atypical cells. Large atypical lymphoid cells showed obvious nucleoli and pleomorphism.
C. Small-to medium-sized lymphoid cells had invaded the glands, resulting in lymphoepithelial lesion (arrow).
D. Neoplastic cells with clear cytoplasm and monocytoid B-cells (arrow).

circumscribed gray-whitish nodule of the right lobe of the thyroid sized 68 cm × 40 cm × 35 cm (Figure 2). Microscopically, a small-to-medium sized atypical lymphocyte occupied the entire resected specimen along with formed lymph follicles (Figure 3A). Most of the atypical lymphocytes showed monotonous proliferation and produced an LEL (Figure 3B), and were mixed with plasmacytoid cells (Figure 3C) and lymph follicles. Immunohistochemical results revealed that the neoplastic cells were positive for CD20 (Figure 4a), CD79a (Figure 4b), and c-IgG and CD138 (Figure 4c), and negative for CD5, CD56, bcl-6, cyclind-D1, and c-IgD. Based on the histological and immunohistochemical findings, the diagnosis was MALT lymphoma. Metastasis was seen throughout the paratracheal lymph node and marginal zone B-cell lymphoma-like features were shown.

One year after the initial operation, post-operative follow-up CT findings of the residual thyroid showed it to be swollen, which suggested recurrence of MALT lymphoma. However, the patient refused intensive therapy and observations were continued as annual check-ups without medication. The patient noticed rapid enlargement of the cervix at five years after surgery, and the left deep cervical lymph node and accessory lymph node were found to be enlarged in follow-up CT findings (Figure 5), leading to suspicion of recurrence of MALT lymphoma. She then underwent a left partial thyroidectomy with regional lymph node dissection.

The tumor was 3 cm × 2.5 cm in size. In gross findings, the cut surface of the resected specimen was replaced by a white-grayish nodule (Figure 6). Microscopically, nodules were occupied by neoplastic cells and lymph follicles including a germinal center

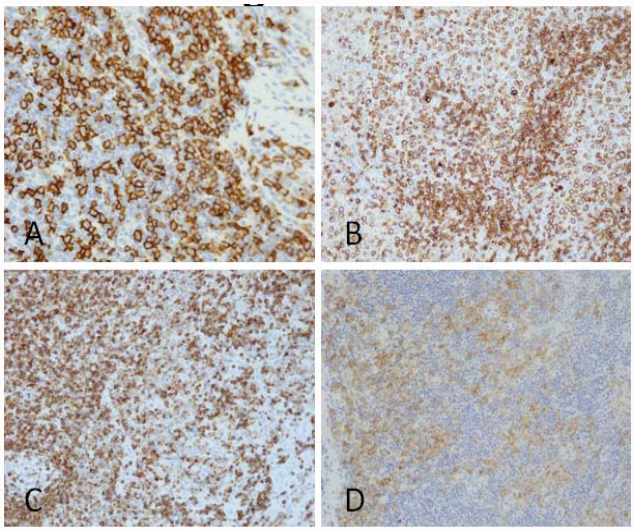

Figure 8: Immunohistochemical features of resected specimen obtained during second operation. (A) CD20, (B) CD79α, (C) bcl-2, and (D) IRTA-1.

were occasionally seen, while nodular proliferation of large atypical lymphoid cells containing mitotic figures surrounded by small-to-medium sized atypical cells were also noted (Figure 7A). Large atypical lymphoid cells showed obvious nucleoli and pleomorphism (Figure 7B). Also, small-to-medium lymphoid cells had invaded glands, namely, an LEL (Figure 7C). In addition, clusters of neoplastic cells with clear cytoplasm (monocytoid B-cells) were often seen (Figure 7D). Immunohistochemical results showed CD20, CD79α, bcl-2, MUM1p, and IRTA-1 to be positive, and CD21, CD10, and bcl-6 as negative (Figure 8). A diagnosis of DLBCL, non-germinal center type; non-GCB was determined. The presence of an LEL and monocytoid B-cells, and immunohistochemical IRTA-1 expression suggested that the DLBCL in this case had originated from MALT lymphoma.

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