Case Report

Mucosa-Associated Lymphoid Tissue Lymphoma with Large Cell Transformation on the Background of Hashimoto’s Thyroiditis: A Case Report and Review Literature

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Primary thyroid lymphoma (PTL) is a rare cause of malignancy that occurs in 0.5% of cases with Hashimoto’s thyroiditis. The most common subtype is diffuse large B-cell lymphoma (DLBCL), followed by mucosa-associated lymphoid tissue (MALT) lymphoma. We described the case of a 70-year-old man who was diagnosed with MALT lymphoma in the background of autoimmune thyroiditis with focal area of DLBCL transformation. The patient was a 70-year-old man with rapidly growing mass of the thyroid gland with compressive symptom over two months. The laboratory data revealed primary hypothyroidism with positively anti-thyroid antibodies. The computerized tomography scan showed right thyroid mass extended to anterior mediastinum and compressed adjacent airway with multiple cervical and mediastinal lymphadenopathies. The pathology from incisional biopsy showed extranodal marginal zone B-cell lymphoma of MALT lymphoma with large cell transformation. The patient received four courses of systemic chemotherapy combined with involved field radiation therapy. The mass was dramatically decreased in size after treatment, leading to a complete resolution of compressive symptoms. Thyroid lymphoma is quite rare; however, the incidence may be higher in patients with Hashimoto’s thyroiditis. A rapidly growing thyroid gland should be considered as PTL. Chemotherapy and radiation are the mainstays of treatment.

Keywords: Mucosa-associated lymphoid tissue lymphoma, Large cell transformation, Diffuse large B-cell lymphoma, Primary thyroid lymphoma, Hashimoto’s thyroiditis

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Primary thyroid lymphoma (PTL) is a rare cause of malignancy, accounting for approximately 2-8% of all thyroid malignancies and 1 to 2% of all extranodal lymphomas(1-5). The annual incidence rate is estimated to be 2.1 per million persons. Women are more predominately affected two to eight times than men(6). Typically, patients present in the sixth or seventh decade of life(7,8). Most PTL is non-Hodgkin’s lymphomas (NHL) of B cell origin. Occasionally T-cell lymphomas have been reported(9). The most common subtype of PTL is diffuse large B-cell lymphoma (DLBCL) followed by a less invasive form named mucosa-associated lymphoid tissue (MALT) lymphoma(5,8,10). The pathological diagnosis of PTL in Hashimoto’s thyroiditis includes MALT lymphoma (47%), DLBCL (43%), and DLBCL with MALT lymphoma (8%)(11). Since MALT lymphoma can progressively transform to be DLBCL, both tumors type can be found within the same thyroid gland in one third of cases(12). Most cases of PTL arise in a background of thyroiditis approximately 60 to 90% of PTL cases(5,6,11,13). MALT lymphoma and PTL tend to arise in the thyroid gland, which has the pathology of Hashimoto’s thyroiditis. Evidence shows that MALT lymphoma and PTL occur in 0.5% and 0.3% of the cases with long-standing Hashimoto’s thyroiditis respectively(11,14,15). According to the previous studies, the average onset of PTL after Hashimoto’s thyroiditis is 4 to 9 years (range 1-362 months)(6,11,13). In addition, the concurrent diagnosis of PTL and Hashimoto’s thyroiditis is 0.3% in the first visit(11).

The typical clinical presentation includes an enlarging neck mass, dysphagia, hoarseness, stridor, dyspnea, and pain. The rapidly enlarging neck mass should be suspected of PTL, and has been reported more than 70% of cases in DLBCL(5,12). One-third of
patients have compressive symptoms. However, B-symptoms, mostly presented in lymphoma, are less common occurrence in 10% of patients\(^{(10)}\). The symptoms of hypothyroidism related to Hashimoto’s thyroiditis are presented only in one-half of patients before the clinical manifestation of PTL\(^{(6,14,16)}\). The diagnosis is difficult based on the morphological and clinical characteristics. Southern blot, flow cytometry, and polymerase chain reaction (PCR) are needed to confirm the diagnosis\(^{(17)}\). In the present study, we described a 70-year-old man who was diagnosed as MALT lymphoma in the background of autoimmune thyroiditis with focal area of DLBCL transformation.

**Case Report**

A 70-year-old man without previous history of goiter was referred to our hospital for further evaluation of a rapidly growing mass of thyroid gland associated with gradually increased difficulty to breathe and swallow over two months. He denied palpitation, fatigue, cold or heat intolerance, hoarseness, fever, night sweats, and weight loss. Vital signs were normal. The neck examination revealed a smooth surface, firm, fixed, non-tender thyroid gland, and the right lobe was larger than left lobe. The estimated size was approximately 80 grams. Pemperton’s sign was negative. Laboratory evaluations revealed high thyroid stimulating hormone (TSH) level of 85.12 uU/ml (normal range 0.27-4.2 uU/ml), low free T3 level of 0.08 ng/dl (normal range 0.18-0.46 ng/dl) and low free T4 level of 0.3 ng/dl (normal range 0.9-1.7 ng/dl). Anti-thyroid peroxidase antibodies were positive (158.3 IU/ml, normal range 0-40 IU/ml) but anti-thyroglobulin antibodies were negative (55.6 IU/ml, normal range 0-125 IU/ml). An initial diagnosis of Hashimoto’s thyroiditis was made and levothyroxine therapy was started. The ultrasound and computerized tomography (CT) scan of the neck, chest, and abdomen showed right thyroid mass extended to anterior mediastinum approximately 10x16 cm\(^2\). The adjacent airway was displaced to the left. Multiple cervical and mediastinal lymph nodes were significantly detected. No distant metastasis was detected. A fine needle aspiration (FNA) biopsy of right thyroid mass was performed, and it revealed a mixed population of lymphoid cells. Most of the cells were immunoreactive with cluster of differentiation (CD) antigen-20. The incisional biopsy was done and the pathology showed extranodal marginal zone B-cell lymphoma of mucosa associated lymphoid tissue (MALT) lymphoma with focal area of large cell transformation (Fig. 1). The

![Fig. 1](image)

**Fig. 1** The thyroid pathology. 1) Mucosa-associated lymphoid tissue lymphoma involving thyroid gland arising in background of chronic lymphocytic thyroiditis. The residual thyroid follicles are separated by the neoplastic lymphocytes; thyroid follicles (arrow), and neoplastic lymphoid cells (arrow head). 2) Area of large cell transformation of MALT lymphoma. 3) The neoplastic marginal zone cells infiltrate into thyroid follicle, forming lymphoepithelial lesion making; neoplastic lymphoid cells (arrow).
immunohistochemical stains revealed CD20(+), CD5(-), CD10(-), CD23(-), Bcl-6(-), CyclinD1(-) and Ki-67 of 50% in the area of large cell transformation (Fig. 2). Bone marrow biopsy reported hypocellular marrow correlated with aging without evidence of lymphoma involvement. The diagnosis was primary thyroid MALT lymphoma with large cell transformation on the background of Hashimoto’s thyroiditis. According to Ann Arbor staging for PTL(18,19), this patient was stage IIEx. Because of its aggressive nature of large cell transformation, the patient received multiagent chemotherapy consisted of Cyclophosphamide, Doxorubicin, Vincristine, Prednisolone in combination with Rituximab (R-CHOP). Four courses of R-CHOP combined with involved field radiation therapy (RT) at the bulky diseases were performed. After treatment, the mass was dramatic response and complete resolution of compressive symptoms.

**Discussion**

The present report referred to a patient with thyroid MALT lymphoma with large cell transformation on the background of Hashimoto’s thyroiditis. The most striking clinical feature in this patient’s presentation was rapid, non-tender enlargement of the thyroid. This is a characteristic feature of thyroid lymphoma(20). Compressive symptoms, seen in up to 30% of patient(6), were found in our patient. The thyroid lymphoma usually presents in the elderly like this patient. Additionally, woman is more common while our case is a man. But men with thyroid MALT lymphoma exhibit a worse prognosis, compared to the well differentiated thyroid cancer(21,22,17). The laboratory data support the diagnosis of Hashimoto’s thyroiditis, which seems to be a risk factor for the development of thyroid MALT lymphoma(11,14). MALT lymphoma itself can turn to DLBCL and is found together about 30%(12). The concurrence of thyroid MALT lymphoma and Hashimoto’s thyroiditis makes the diagnosis of lymphoma more difficult.

In Hashimoto’s thyroiditis, the pathological finding includes small lymphocytes, Hurthle cells, florid lymphoid hyperplasia with expanded germinal centers and increased interstitial connective tissue. However, MALT lymphomas can have a heterogeneous appearance but are generally high cellularity, with a prominent population of intermediate-sized lymphoid cells, lymphoepithelial lesions, reactive lymphoid follicle as well as a large plasma cell component. DLBCL appears uniformly large, abnormal lymphoid cells with lymphoepithelial foci and decreased or absent colloid(21-23). There are still challenges in FNA diagnosis of thyroid lymphoma, particularly due to the histological similarities with thyroiditis and the high

**Fig. 2** The immunohistochemical stains. The neoplastic cells express CD 20 but have no reactivity to CD3, CD5, CD23, and Cyclin-D1. The Ki-67 labeling index approaches 50% (left) and less than 30% (right) of area of large cell transformation.
coincidence of these pathologies within the same gland, resulted in the increased false-negative rates from sampling error. The immunohistochemistry has improved the accuracy of cytology in diagnosing lymphoma. No specific immunohistochemical marker has yet been identified for MALT lymphoma, but evaluation of a panel of immunohistochemistry is necessary for assessment of the architecture of the lymphoid infiltrate, lineage assignment, and for the exclusion of other lymphomas. The presence of B-cell antigens such as CD19 and CD20 helps to identify a B-cell lineage of the lymphoid cells. The presence of an extensive, dense, diffuse infiltration of CD20(+) B cells between thyroid glands is highly suggestive of lymphoma. Moreover, immunohistochemistry was helpful in excluding follicular lymphoma, which exhibits a CD10 marker. Negative results of CD5, CD10, CD23, CyclinD1, and BCL-6 can be helpful to exclude other small B cell lymphomas such as chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), follicular lymphoma, and mantle cell lymphoma. Staining for CK demonstrates the lymphoepithelial lesions and remnants of epithelial cell. The Ki-67 is low in MALT lymphoma but high in area of large cell transformation. In our case, pathology revealed intermediate-sized lymphoid cells with lymphoepithelial lesion, stained by CK that meant MALT lymphoma. It was confirmed as B-cell in origin by immunoreaction with CD20. In the same gland, tissue also showed large-sized abnormal lymphoid cells in transformation, referred to DLBCL. In addition, the Ki-67 labeling index approaching 50% in area of large cell transformation prefers DLBCL than MALT lymphoma, which Ki-67 approaches less than 30% (Fig. 2). The staging was made by CT scan of neck to abdomen and bone marrow biopsy resulting stage IIIE (E: extranodal origin, X: bulky >10 cm). When determining a treatment plan, the histology and staging need to be considered. There are no randomized, controlled trials evaluating the efficacy of different treatment options in PTL; therefore, the current evidences are mostly derived from retrospective studies and from the studies of extranodal NHLs. However, with high relapse rates, low survival rates, and the realization that thyroid lymphoma is sensitive to chemotherapy and radiation making surgery play a limited role. Among those with aggressive PTL either stage IE or IIE, like this patient, the combined modality treatment (CMT) significantly improved overall survival (OS), disease-free survival and local control more than those of either RT or chemotherapy alone. The addition of Rituximab to CHOP improved OS compared with CHOP alone. Matsuzuka et al, described a report of 119 patients with intermediated grade, stage IIE PTL treated with six courses of CHOP combined with RT had 100% survival rate at 8 years. Surgery in aggressive disease is used for improvement of compressive symptom or protection of the airway.

Conclusion

The present case demonstrated a male patient with MALT lymphoma with large cell transformation on the background of Hashimoto’s thyroiditis. Thyroid lymphoma is quite rare; however, the incidence is higher in patients with a history of Hashimoto’s thyroiditis. A rapidly growing thyroid gland should be considered of lymphoma of the thyroid as a diagnosis. Diagnosis can be made by FNA with immunohistochemistry to improve accuracy. Chemotherapy and radiation are the mainstays of treatment.

What is already known on this topic?

PTL is a rare cause of thyroid malignancy and extranodal lymphoma. It should be suspected in patient with rapidly enlarging neck mass especially with a history of Hashimoto’s thyroiditis. The most common subtype of PTL is DLBCL, followed by MALT lymphoma. MALT lymphoma can transform into DLBCL and occurs in the cases of Hashimoto’s thyroiditis. Wanatabe et al, reviewed 171 patients with PTL and 24,553 patients with Hashimoto’s thyroiditis. The pathological diagnosis included DLBCL 43%, MALT lymphoma with DLBCL 8%, MALT lymphoma 47% and others 2%. That means, MALT lymphoma with DLBCL is a rare pathology of PTL in Hashimoto’s thyroiditis patient.

What this study adds?

This patient showed the MALT lymphoma with large cell transformation of DLBCL in the same gland of Hashimoto’s thyroiditis background. Patient with rapidly enlarging neck mass should be suspected of PLT. Majority of patient will come with compressive symptom and positively Pemperton’s sign. However, this case had right thyroid mass extending to anterior mediastinum approximately 10x16 cm² without the sign of Pemperton. A FNA biopsy of right thyroid mass revealed a mixed population of lymphoid cells, but the incisional biopsy showed extranodal marginal zone B-cell lymphoma of MALT lymphoma with focal area.
of large cell transformation. There are still challenges in FNA diagnosis of thyroid lymphoma, particularly due to the histological similarities with thyroiditis and the high coincidence of these pathologies within the same gland, resulted in the increased false-negative rates from sampling error. The immunohistochemistry is helpful.

Potential conflicts of interest
None.

References


