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Primary thyroid lymphoma

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ABSTRACT

Primary thyroid lymphoma is an uncommon thyroid malignancy. The treatment modalities significantly differ from other thyroid malignancies. Frequently it is accompanied by Hashimoto's thyroiditis, and it may be difficult to differentiate the two entities histologically. Patients typically present with suddenly growing mass in the thyroid gland. Discrimination between primary and secondary lymphoma is important due to variations in diagnostic tools, treatment modalities and prognosis. Surgery, chemotherapy, radiotherapy or combinations of these modalities may be applied in treatment. In this report, three cases with primary thyroid lymphoma in which three different treatment modalities have been applied are presented.

Keywords: Thyroid, primary, lymphoma, thyroidectomy

INTRODUCTION

Primary thyroid lymphoma (PTL) constitutes 0.5-5% of all thyroid malignancies and about 2% of extranodal lymphomas. Its incidence is two per million persons (1). It is 2-8 times more common in women than in men. Patients usually present with rapidly growing masses in the thyroid gland in their sixth-seventh decades. The disease is frequently accompanied by chronic Hashimoto's thyroiditis. Hashimoto's thyroiditis is known to increase the risk of lymphoma (2). Most tumors are B-cell derived non-Hodgkin's lymphoma. Distinction between primary-secondary lymphoma is important due to the difference in both prognosis and therapy.

Treatment and prognosis varies according to histology and stage. Treatment options include surgery, radiotherapy, chemotherapy and their combination. Three cases with primary thyroid lymphoma are presented in this article.

CASE PRESENTATIONS

Case 1

A 71-year-old female patient who has been followed-up for nodular goiter for the past 5 years was admitted with progressive shortness of breath and hoarseness within the last month. The patient had hypertension and chronic bronchitis and lost 5 kg in the last three months. Thyroid function tests were within normal limits. Thyroid ultrasound (US) revealed a 52 mm in size, irregular bordered hypoechogenic nodule with milimetric calcifications that completely occupied the right lobe, isthmus and half of the left lobe. There were no pathologic lymph nodes. The nodule was hypoactive on scintigraphy. Fine needle aspiration biopsy (FNAB) of the nodule showed lymphocytic thyroiditis on a background of colloid nodules. The computed tomography of the chest revealed retrosternal goiter and interstitial lung disease.

A total thyroidectomy was performed with a preliminary diagnosis of nodular goiter. The right lobe size was 7 x 6 x 8 cm, and the left lobe was 10 x 8 x 9 cm. The frozen section evaluation during surgery revealed malignant tumor infiltration suspicious for anaplastic carcinoma or malignant lymphoma. Postoperative histopathologic diagnosis was reported as high-grade neoplastic B-cell infiltration. Morphological findings also implied Burkitt lymphoma but immunophenotyping (CD 10 negativity and focal/weak Bcl-2 expression) did not support this diagnosis. The results were evaluated as B-cell lymphoma, unclassifiable, with features intermediate between Burkitt lymphoma and diffuse large B-cell lymphoma (DLBCL) in accordance with the 2010 WHO classification.

The postoperative positron emission tomography (PET) performed for staging showed mass lesions that combined with each other, starting from the left posterior segment of the oropharynx extending to the left middle-lower cervical, supraclavicular, upper mediastinal and prevascular areas that were hypermetabolic (SUVmax: 50) and were considered malignant. In addition, malignant hypermetabolic lymph nodes were observed in the mediastinum and around the celiac trunk. Bone marrow biopsy was normocellular.

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The patient received 8 cycles of rituximab-cyclophosphamide-vincristine-prednisone (R-CVP) with a diagnosis of primary thyroid DLBCL non-Hodgkin's lymphoma Stage 3EB. There were no pathological findings on post-treatment PET scan, which was interpreted as a response to treatment. The case is being followed-up without recurrence or metastasis at 18 months after surgery.

Case 2

A 39-year-old female patient, who was on thyroid hormone replacement therapy due to hypothyroidism for 8 years, was admitted to our hospital with a rapidly growing swelling in the neck. On physical examination, a 2 cm nodule was detected in the right thyroid lobe. Peripheral lymph node examination was normal. She has discontinued thyroid hormone replacement therapy for the last two years. Blood thyroid stimulating hormone level was 29 µIU/mL (normal range of 0.5-5 µIU/mL), anti-thyroid peroxidase and anti-thyroid antibody levels >1000 IU/mL (normal range: 0 to 5.61 IU/mL and 0 to 4.11 IU/mL, respectively). The size of the right thyroid lobe on ultrasound was 33 mm, the left lobe 26 mm, and heterogeneity, isoechogenic areas with thyroid parenchyma and no central vascularity were viewed that were consistent with thyroiditis. There were no pathologic lymph nodes. The FNAB of the right lobe was evaluated as lymphocytic thyroiditis with papillary carcinoma Hurthle cell variant.

The patient underwent total thyroidectomy. During surgery, the thyroid was firm, attached to the surrounding tissues and was fibrotic. Right thyroid lobe size was 9 x 4 x 3 cm, and left lobe dimensions were 5 x 3 x 3 cm. Frozen section study of the central lymph nodes were reported as benign. Postoperative histopathologic evaluation revealed morphologic and immunophenotypic findings consistent with (CD5 negative, bcl-6 negative, bcl-2 positive) extranodal marginal zone lymphoma (the MALT-type) showing diffuse plasmocytic differentiation. It had findings consistent with Hashimoto's thyroiditis on a background of lymphoid neoplasia. She did not have a history of fever, weight loss or night sweats. Staging tomography showed millimetric lymph nodes in all neck zones. Radiotherapy (3600 cGy) localized to the neck and upper mediastinum was given for localized extranodal lymphoma stage 1E. There were no recurrence or metastasis detected in the 15th postoperative month controls.

Case 3

A 53-year-old female patient who was followed-up for nodular goiter for 15 years was admitted with pain and swelling in the neck and choking for a month. She did not have fever, weight loss or night sweats. She had a hard thyroid nodule about 2 cm in size on physical examination. On ultrasound, there were hyperechoic nodules in both lobes of the thyroid gland and the isthmus, the largest with a diameter of 2.5 cm. Fine needle aspiration biopsy showed suspicious findings for malignancy, hematoproliferative disease, and lymphoid neoplasia. The patient underwent total thyroidectomy. The size of the right lobe was 7 x 4 x 3 cm and that of the left lobe was 7 x 3 x 3 cm. Postoperative histopathologic evaluation showed morphologic and immunophenotypic findings consistent with low-grade B-cell lymphoid neoplasia (extranodal marginal zone lymphoma of MALT-type). There was no evidence of lymphocytic thyroiditis. Staging tomography showed no pathologic findings. No additional treatment was provided. There were no recurrence and metastasis detected in the postoperative 9 month control.

DISCUSSION

Primary lymphoma of the thyroid is a rare but distinct entity from other thyroid neoplasias since its treatment differs. They have different treatment options according to histopathologic subgroups. Typically, they are a disease of the 6-7th decades. Most patients are women. As in our patients, they usually present with a recently growing painless mass. Classic B-type symptoms of lymphoma such as fever, sweating and weight loss are detected in less than 20% of patients (3).

Primary thyroid lymphoma is mostly accompanied by Hashimoto's thyroiditis that is the only identified risk factor, and they can be mistaken for one another on pre-operative cytopathologic examinations. Although Hashimoto's thyroiditis is detected in 80% of primary thyroid lymphomas, only 0.6% of patients with Hashimoto's thyroiditis develop PTL (4). In two of our cases, lymphocytic thyroiditis was detected preoperatively by FNAB. In the patient with no signs of thyroiditis, FNAB was suspicious for lymphoproliferative disease. In one of the cases with lymphocytic thyroiditis on fine needle aspiration biopsy, there was no suspicion of malignancy. The other patient was evaluated as thyroiditis with papillary carcinoma Hurthle cell variant. Although DLBCL is recognized more easily by FNAB with the presence of large atypical cells, our case was evaluated as lymphocytic thyroiditis. FNAB has become more sensitive and specific in recent years with the use of flow cytometry and immunohistochemical studies (5). Tru-cut needle biopsy can be used for diagnosis of PTL and to avoid unnecessary surgery if FNA results are insufficient and if there is no suspicion of anaplastic thyroid cancer within a suddenly growing thyroid mass.

Staging is required for treatment planning in patients with PTL. The staging is performed according to Ann-Arbor classification (Table 1) (6). Although low specificity and high-cost limit the role of positron emission tomography, it is the most convenient method for staging with detection of regional-distant disease and particularly in monitoring response to treatment. Our first case had an aggressive course and postoperative PET was used for staging. The patient was evaluated as stage 3E because of the widespread hypermetabolic lymph nodes in both sides of the diaphragm. No involvement was identified in the control PET obtained after chemotherapy. Computed tomography was used for staging in the remaining patients. In the second case, there were millimetric lymph nodes in the neck. No involvement was detected in the other case. Bone

Table 1. Ann-Arbor classification

Stage 1E	Confined to the thyroid gland
Stage 2E	Locoregional lymph node involvement in addition to thyroid gland
Stage 3E	Involvement of lymph nodes located in both sides of the diaphragm
Stage 4E	Disseminated disease
	A: Absence of symptoms
	B: At least 10% body weight loss over 6 months, fever without an infection over 38 degrees, recurrent night sweats

marrow biopsy is required in high-grade patients or those with suspicion of systemic disease. There was no evidence of bone marrow involvement in our patient with DLBCL.

In our first case, postoperative chemotherapy was given due to DLBCL and diffuse lymph node involvement, our second case received postoperative extended radiotherapy due to millimetric lymph nodes in all neck zones on postoperative tomography, and the third case underwent surgery alone since there was no lymph node involvement. In these cases, cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) is the mainstay chemotherapy protocol. Addition of rituximab to treatment increases disease-free survival and life expectancy in DLBCL (7). However, since the patient had a low ejection fraction, a protocol without anthracycline was decided to be implemented and cyclophosphamide, vincristine and prednisolone were given.

The prognosis of PTL is determined by disease subtype. The five-year life expectancy is 75% for DLBCL and 96% for MALT lymphoma. 5-year life expectancy by stage is 86% for stage 1E, 81% for stage 2E, and 64% for stage 3E-4E (8). Most recurrences develop within the first 4 years. Poor prognostic factors are reported as age, stage, tumor type and size, lymph node involvement, treatment selection, mediastinal involvement, and presence of B symptoms (9). No recurrence or metastasis was detected in our cases during the follow-up period.

CONCLUSION

Primary thyroid lymphoma is a rare condition that can be difficult to diagnose in the preoperative period. Appropriate treatment should be planned according to staging after diagnosis.

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