CASE REPORT
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Rare Concurrence of Triple Primary Thyroid Cancer: A Patient of Papillary Carcinoma, Follicular Carcinoma, and Primary Lymphoma of the Thyroid

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We report a rare case of co-occurrence of papillary thyroid carcinoma (PTC), follicular thyroid carcinoma (FTC) and primary thyroid lymphoma. A 55-year-old woman presented with a large mass in left lobe of thyroid, biopsy confirmed diffuse large B-cell lymphoma. After 4 cycles of rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisolone chemotherapy, positron emission tomography scan revealed markedly decreased in size, but still present. Repeated ultrasonography-guided gun biopsies of 2 lesions indicated Hurthle cell neoplasm. After total thyroidectomy and bilateral central lymph node dissection, residual hypermetabolic lesion of left lobe was determined to be FTC and right lower lesion to be nodular hyperplasia. Besides, a PTC was incidentally detected in left lobe. If there are multiple nodular lesions at diagnosis or there is insufficient response after 1st line chemotherapy for primary thyroid lymphoma, each lesion should be biopsied to confirm its pathological type.

Key Words: Thyroid lymphoma, Papillary thyroid cancer, Follicular thyroid cancer, Triple primary thyroid cancer

Introduction

Papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC) account for 70–80% and 15% of all thyroid cancers, respectively.[1)] Primary thyroid lymphoma is a rare cancer, accounting for an estimated 1–5% of thyroid malignancies and 2% of all extranodal lymphomas. The simultaneous occurrence of these 3 malignancies in the same patient is extremely rare.

Case Report

A 55–year–old woman visited in our clinic because of shortness of breath and the progressive enlargement of a mass in her neck. She had felt the mass in her neck growing for the past 3 months and lost approximately 3–4 kg in weight without fever or night sweating. She denied taking any pills, had no history of thyroid disease, goiter, or radiation therapy to the head or neck, and had no family history of thyroid cancer or other malignancy. On physical examination, a firm nodule about 6 cm in size was palpable in her left thyroid gland moved with deglutition. There was no palpable cervical lymphadenopathy.

Initial thyroid ultrasonography (US) showed a huge mass that was accompanied by 3 small nodules in both lobes with underlying diffuse thyroiditis. The huge 6.4×5.4×3.0 cm lobulated contoured hypoechoic solid mass located in the left thyroid gland and an isoechoic

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1.1×1.1×0.6 cm nodule with calcification in the left upper lobe appeared mostly suspicious. Another isoechoic solid nodule was located in the right lower lobe and measured 0.9×0.8×0.7 cm, appeared likely to be benign. Finally, a 0.7×0.5×0.3 cm hypoechoic nodule was evident in the right thyroid middle lobe (Fig. 1). US-guided gun biopsy of the huge mass in the left lobe revealed a diffuse large B cell lymphoma (DLBL), stained positively for CD20 (+), Bcl-6 (+), and Ki-67 in 60% of cells (Fig. 2).

An initial positron emission tomography (PET) scan detected a hypermetabolic lesion (standardized uptake value [SUV] 27.5) in the left lower neck, otherwise unremarkable. Accordingly, the lesion was classified as Ann Arbor stage IE-A, with an International Prognostic Index of 0. The initial lactate dehydrogenase (LDH) was 181 U/L (normal range, 101-202 U/L), the free T4 1.36 ng/dL (normal range, 0.89-1.79 ng/dL) and the thyroid stimulating hormone (TSH) level 2.79 μIU/mL (normal range, 0.17-4.05 μIU/mL) were both within normal ranges.

After 4 cycles of rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone (R-CHOP) chemotherapy, PET scanning revealed that the hypermetabolic nodule in the left thyroid had decreased in size, but still present (SUV 8.4). Scanning also showed the mild hypermetabolic lesion in the right lower lobe, which appeared to have a non-specific uptake. Otherwise, no gross abnormal uptake was evident, suggesting no additional malignant processes. After 8 cycles of R-CHOP chemotherapy, PET scanning showed no major changes from the previous status (Fig. 3). The diminished, residual hypermetabolic nodular lesion (SUV 6.6) in the left thyroid and the mild hypermetabolic lesion (SUV 3.9) in the right lower lobe remained evident. We rechecked thyroid function and autoantibody levels. Thyroid function remained within the normal ranges (free T4 1.4 ng/dL, TSH 1.61 μIU/mL), but the microsomal antibody titer was 101 U/mL (normal range,

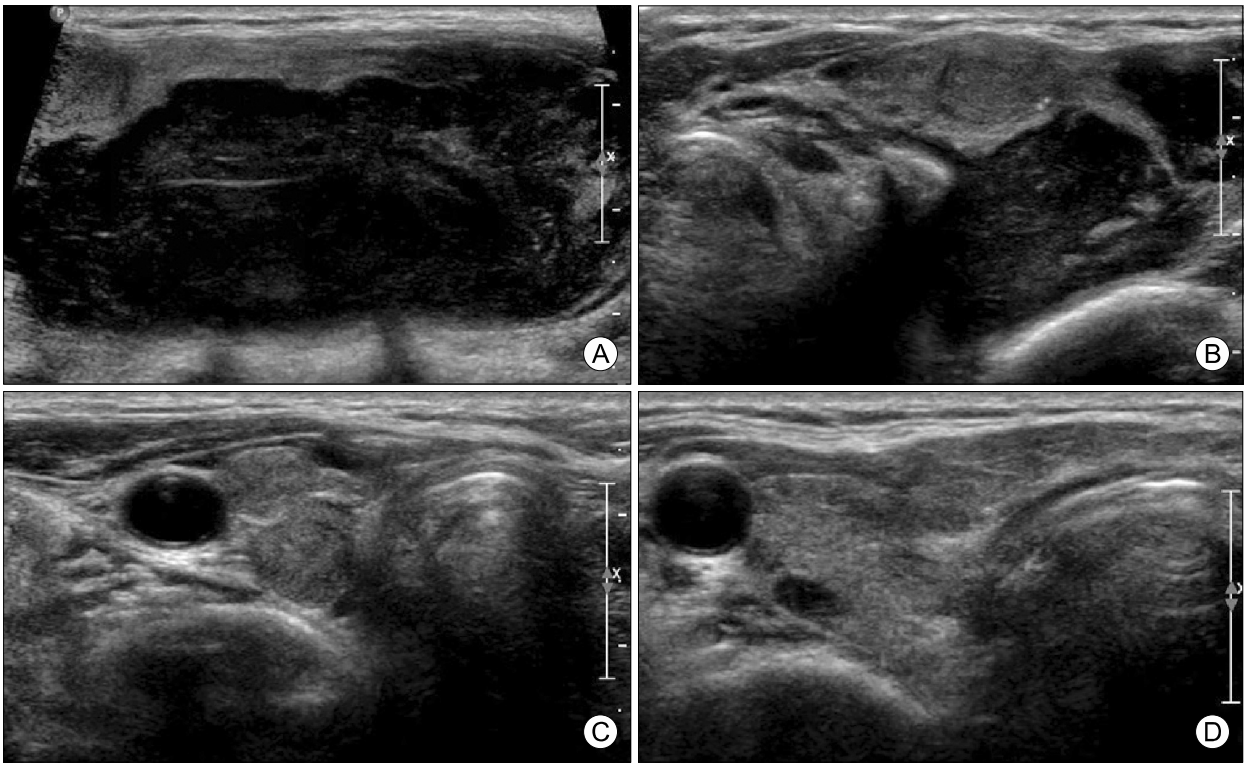

Fig. 1. Initial ultrasonography of thyroid. A huge lobulated contoured hypoechoic solid mass in left thyroid gland, measured 6.4×5.4×3.0 cm (A), isoechoic solid mass with calcifications in left thyroid gland upper pole, measured 1.1×1.1×0.6 cm (B), isoechoic solid nodule in right thyroid gland lower pole, measured 0.9×0.8×0.7 cm (C), hypoechoic solid nodule in right thyroid middle lobe, measured 0.7×0.5×0.3 cm (D).

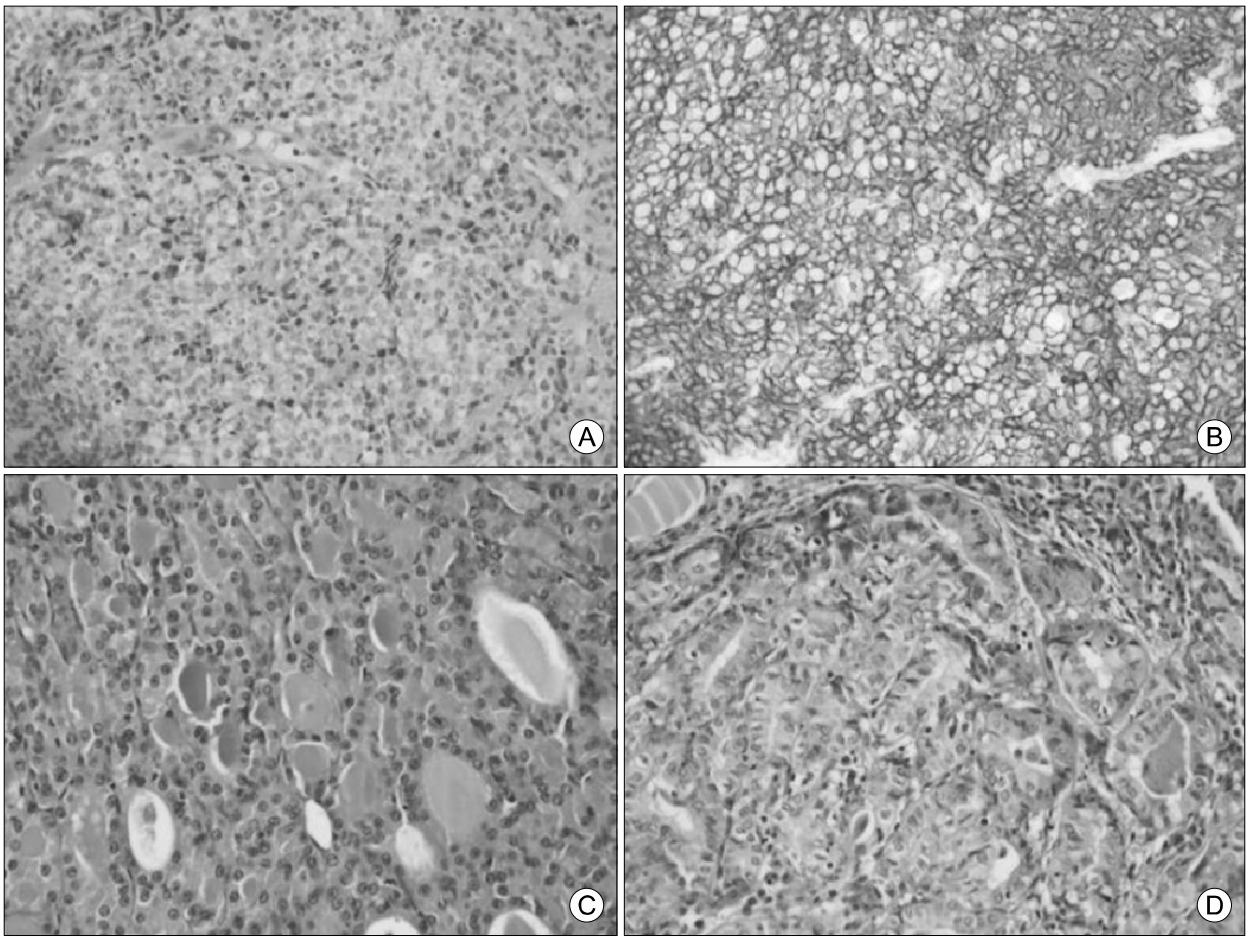

Fig. 2. Pathologic examination of thyroid lymphoma obtained by core needle biopsy (Hematoxylin & Eosin stain) (A) and immunohistochemical examination of CD20 of primary thyroid lymphoma (B); (×400), follicular thyroid cancer (C) and papillary thyroid carcinoma (D) collected by surgical resection (Hematoxylin & Eosin stain; ×400).

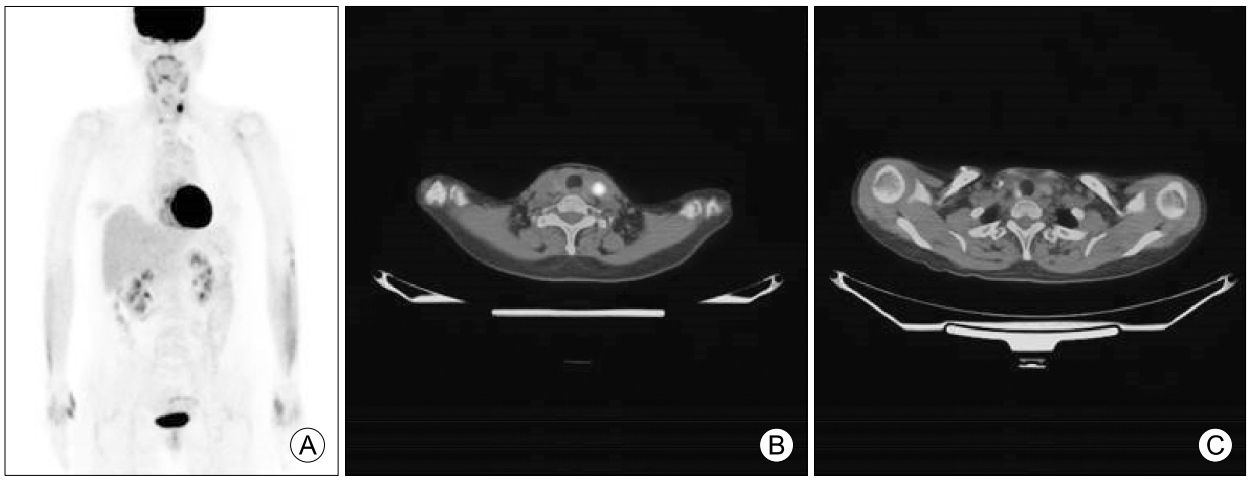

Fig. 3. PET scan image after 8th chemotherapy of rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone (R-CHOP) (A), residual hypermetabolic nodular lesion (SUV 6.6) in the left thyroid (B), mild hypermetabolic lesion (SUV 3.9) in the right lower lobe (C).

0–100 U/mL), suggesting Hashimoto's thyroiditis.

The repeated US result revealed the 3 small nodules showed no change: the 1.1×1.0×0.8 cm hypoechoic solid nodule with microcalcification in the left upper lobe, the 0.9×0.8×0.6 cm isoechoic nodule in the right lower lobe, and the small 0.5×0.3×0.2 cm hypoechoic nodule in the left upper pole medial aspect. The 2 nodules in the left upper and right lower lobes were pathologically confirmed as Hurthle cell neoplasms using gun biopsy. A total thyroidectomy with bilateral central lymph node (LN) dissection was performed. During the operation, a moderate degree of fibrotic change was observed in the left paratracheal area, related to Hashimoto's thyroiditis or a chemotherapy-induced change. In addition, several regional LNs were enlarged.

Histopathological examination identified the 1.2×0.9×0.7 cm minimally invasive follicular carcinoma in the left upper lobe, which had minimal capsular invasion (pT1bN0; delphian LN: 0/2, left level VI LN: 0/4, right level VI LN: 0/4) and did not involve hemorrhage or necrosis (Fig. 2C). The nodule in the left upper pole medial aspect was confirmed to be a 0.3×0.2×0.2 cm occult papillary microcarcinoma, without vascular or lymphatic invasion and extrathyroidal extension (Fig. 2D). Finally, the hypoechoic nodule in the right lower lobe, thought to be a Hurthle cell neoplasm based on a gun biopsy specimen, was confirmed to be nodular hyperplasia.

Immunohistochemical staining of the FTC of left lobe for galectin-3, cyclin D1, and anti-human mesothelial cell antibody were all positive. The *BRAF* mutation wasn't detected in the PTC tumor on reverse transcription-polymerase chain reaction. The patient discharged with 0.15 mg/day levothyroxine, and didn't undergo remnant iodine ablation.

Discussion

This patient was at first diagnosed with primary thyroid lymphoma alone, but additionally diagnosed with FTC and PTC after chemotherapy. The co-occurrence of lymphoma and other thyroid cancers is rare. One case has been reported a 59-year-old man with known Hashimoto's thyroiditis, presented with a rapid enlargement of the thyroid gland over few months.[2,3] In this case, pathology indicated a PTC and an extranodal marginal zone B-cell lymphoma of the mucosa-associated lymphoid tissue (MALT) type. Another case involved a 61-year-old man, presented with a rapid enlargement of the thyroid gland over 3 months[2,3] Pathology showed multicentric PTCs with a concomitant thyroid MALT lymphoma. In the present report, we have described the first case of a triple primary thyroid cancer, of concomitant PTC, FTC, and primary thyroid lymphoma.

The treatment of choice for primary thyroid lymphoma has evolved over the past few decades. Graff-Baker et al.[4] analyzed 1408 cases of primary thyroid lymphoma, found that surgery and radiation for primary thyroid lymphoma have declined over the years, while chemotherapy has recently become more preferred. Current treatment recommendations for primary thyroid lymphoma are histology-specific. For example, surgery or radiation is preferred for the initial treatment of MALT lymphomas, whereas R-CHOP chemotherapy is recommended as the first treatment for DLBL. Doria et al.[5] suggested that combined chemoradiation therapy should be the mainstay of treatment for primary thyroid lymphoma. The choice of chemotherapy regimen has, for primary thyroid lymphomas, been extrapolated from studies of extranodal lymphomas.

However, controversy remains concerning the role of thyroid surgery for early stage thyroid lymphoma especially when it occurred with thyroid carcinoma. A study of 62 patients from the Mayo Clinic concluded that thyroidectomy with adjuvant chemotherapy resulted in long-term cure in patients with primary thyroid lymphoma. Meyer-Rochow et al.[6] suggested that operations should only be performed to establish the diagnosis of primary thyroid lymphoma or to manage severe obstruction of the airway. Some practitioners[7] have recommended that fine needle aspiration and adjuncts should be the initial tests that are used to diagnose thyroid lymphoma, although open surgical biopsy may still be required in many cases. To date, however, there have been no published investigations regarding the optimal management of multiple thyroid

nodules adjacent to primary thyroid lymphoma. In the present case, we incidentally found differentiated thyroid carcinoma during chemotherapy for DLBL, which was localized within the thyroid. Because the biopsy specimen indicated Hurthle cell neoplasm, which suggests neither malignancy nor benign nodule can be differentiated by biopsy, we performed surgical resection. Based on our experience with this case, the precise pathologic confirm of multiple nodules should be done first, and if there is any suspicious finding, surgery can be performed before chemotherapy. Hashimoto's thyroiditis increases an incidence of the primary thyroid lymphoma.[8] Moreover, Kim et al.[9] reported that Hashimoto's thyroiditis is a strong risk factor for differentiated thyroid cancer (DTC), specifically with PTC. So in case of Hashimoto's thyroiditis patients, if multiple nodules are found, biopsies for each nodular lesion should be performed to confirm if there are any possibility of hidden malignancy.

The management of co-occurring cancers should be considered separately, and the patient's prognosis is probably dominantly affected by the cancer that has the worst prognosis.[3,10-14] If there is insufficient response after 1st line chemotherapy for primary thyroid lymphoma, each residual lesion should be biopsied to confirm its pathological type, since the response rate of R-CHOP chemotherapy to DLBL is excellent, over 80% in stage I. In cases that involve the simultaneous occurrence of multiple thyroid neoplasms, surgery can be considered as standard of care.[3]

Conflict of Interest

Conflict of interest relevant to this article was not reported.

Acknowledgments

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