CASE REPORT

Commonly forgotten complication of Hashimoto's thyroiditis

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SUMMARY

Hashimoto's thyroiditis (HT) is a frequently encountered condition in clinical practice and management is generally uncomplicated with patients on a stable dose of thyroxine supplementation. However, complications of thyroid lymphoma can develop, though it is rare and hence commonly forgotten by physicians. We present a case of a patient with HT who developed thyroid lymphoma. A 61-year-old woman presented with an enlarged goitre complicated by compressive symptoms and was diagnosed with HT. She was treated with stable dose of thyroxine but her constitutional symptoms of weight loss prompted further investigations and diagnosis of diffuse large B-cell lymphoma was eventually made. She underwent chemotherapy and adjuvant radiotherapy and is currently in remission 1 year post-treatment. There should be an increased index of suspicion of primary thyroid lymphoma in patients with HT for early diagnosis and treatment for better outcomes.

BACKGROUND

Hashimoto's thyroiditis (HT) is a frequently encountered condition in clinical practice and is the most common cause of hypothyroidism in iodine-sufficient areas. Management is generally uncomplicated and patients are usually well on a stable dose of thyroxine supplementation.

However, complications of thyroid lymphoma can develop though it is rare and hence commonly forgotten by physicians. We present a case of a patient with HT who developed thyroid lymphoma.

CASE PRESENTATION

A 61-year-old Chinese woman was first diagnosed with HT when she presented to her primary care physician with a 1-year history of gradually enlarging goitre. At diagnosis, her free thyroxine level (fT4) was normal at 14.8 pmol/L (11.9–24.6 pmol/L), thyroid stimulating hormone elevated at 5.37 mIU/L (0.27–4.20 mIU/L) and antithyroid peroxidase antibody elevated at 277 IU/mL (5–34 IU/mL). No ultrasonography was performed initially as the goitre was thought to be secondary to HT. She was then started on thyroxine replacement with normalisation of her thyroid function. Six months later, she was referred to the endocrinology department by her primary care physician for an ultrasonography and fine-needle aspiration (FNA) as her goitre was rapidly enlarging and was associated with compressive symptoms of dysphagia. She had loss of weight of 9 kg over the past 6 months but otherwise was well with

no other constitutional symptoms such as fever, chills or rigors. She had no significant medical or surgical history of note. There was no prior history of head and neck radiation and no family history of malignancies.

On examination, the patient was afebrile with a non-toxic appearance. Her heart rate was 75 bpm and blood pressure 143/63 mm Hg. There was a hard mass over the left side of the neck with no palpable cervical lymph nodes. The rest of the examination of the cardiopulmonary, abdominal and neurological system was unremarkable.

INVESTIGATIONS

On presentation, her thyroid function was normal. An ultrasound scan of the neck ([figure 1](#)) revealed a lobulated heterogeneous mass measuring 5.5×3.2×2.9 cm with internal vascularity and echogenic specks. CT scan of the neck performed subsequently revealed a 6.7×7.0×4.1 cm mass. Infiltration of the postcricoid region was seen, together with left thyroarytenoid muscle involvement. There was also possible infiltration through the left lateral tracheal wall and possible encasement of the left common carotid artery ([figure 2](#)). FNA and subsequent ultrasound-guided core biopsy of the left thyroid mass showed atypical cells, suspicious of derivation from a lymphoma. She underwent another open biopsy of the left thyroid mass and cervical lymph node. Pathological examination and immunohistochemical staining performed on the left thyroid mass showed sheets of medium-sized to large CD20+ lymphoid cells, consistent with diffuse large B-cell lymphoma (DLBCL) ([figures 3](#) and [4](#)). Lymph node histology showed clusters of large CD 20+ lymphoid cells with irregular pleomorphic nuclei and multiple nucleoli within the subcapsular sinuses and nodal parenchyma ([figure 5](#)). Bone marrow examination showed no lymphomatous involvement. Staging CT scans of the thorax, abdomen and pelvis revealed a small 0.4 cm superior mediastinal lymph node with no other significant lymphadenopathy or masses elsewhere.

TREATMENT

Stage IIE DLBCL of the thyroid gland with background HT was diagnosed in view of regional lymph node involvement. She was seen by the medical oncologist and underwent six cycles of chemotherapy with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP) with good response. A full body fluorodeoxyglucose-positron emission tomography

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Figure 1 Ultrasound scan of the neck showing a lobulated heterogeneous mass with internal vascularity and echogenic specks.

(FDG-PET)/CT scan postsix cycles of R-CHOP showed significant decrease in FDG uptake in the thyroid suggestive of treated disease. She also underwent adjuvant radiotherapy in view of initial bulky disease.

OUTCOME AND FOLLOW-UP

Currently she is maintained on thyroxine 75 µg daily and remains euthyroid and disease-free at her review 1 year after completion of chemotherapy and radiotherapy.

DISCUSSION

Primary thyroid lymphomas (PTL) are rare and constitute 1–2% of all extranodal lymphomas¹ and ~1–5% of all thyroid malignancies.² Most PTL are non-Hodgkin's lymphomas and the two most common subtypes include DLBCL (>50% of cases) and extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT) lymphoma (10–23%). The less common subtypes include follicular lymphoma (10%), small lymphocytic lymphoma (3%), Hodgkin's lymphoma (2%), Burkitt lymphoma, T-cell lymphoma, mantle cell lymphoma and lymphoblastic lymphoma (each <1% of cases).³ DLBCL are aggressive with almost 60% of diagnosed patients having

Figure 2 CT scan of the neck showing a thyroid mass with possible infiltration through the left lateral tracheal wall and possible encasement of the left common carotid artery.

Figure 3 A high-power view revealing an infiltrate of large lymphoid cells replacing the thyroid tissue associated with nuclear pleomorphism (H&E, original magnification ×400).

disseminated disease at presentation while MALT lymphomas have a relatively indolent course. Of note, MALT lymphoma can transform into DLBCL with clinical behaviour similar to that of DLBCL.⁴ PTL affects middle-aged to older individuals and women are more commonly affected than men, with the ratio of occurrence ranging from 2:1 to 8:1. Patients with pre-existing HT have more than a 60-fold risk of developing thyroid lymphoma,⁵ like in our patient. Patients most commonly present with a rapidly enlarging goitre, but compressive symptoms, cervical lymphadenopathy and even B symptom like fever, sweats and weight loss can occur. Duration of symptoms before diagnosis range from a few days to 36 months, with a shorter duration reported in those with DLBCL.³ In our patient, the symptoms of compression occurred over 2–3 weeks.

HT plays an important role in the development of thyroid lymphoma. The prolonged antigenic stimulation of the lymphocytes in the setting of autoimmune thyroiditis predisposes the normal cells to lymphomatous transformation and subsequently to a lymphoid malignancy. Malfunction of the somatic hypermutation process, which is regarded as a mechanism of lymphomagenesis, has recently been shown in PTL and in non-neoplastic B-cells from chronic lymphocytic thyroiditis. These findings indicate that aberrant somatic hypermutation

Figure 4 Antibody for CD20 decorating the tumour cells, thereby confirming a diagnosis of large B-cell lymphoma (Ventana optiview, original magnification ×400).

Figure 5 Examination of the lymph node at high power revealed partial involvement by the neoplastic lymphoid cells (H&E, original magnification $\times 400$).

process represents an early event in the process of B-cell clonal transformation.^{6 7}

It was previously studied that a long duration of ~ 20 years of HT increases the risk of developing thyroid lymphoma.⁸ However, some small studies have found that the interval between the diagnosis of HT and that of thyroid lymphoma may be shorter, about 4–9 years.^{9 10} This is also supported by a recent Japanese study which found that the median interval between diagnosis of HT and thyroid lymphoma was 18 months,¹ like in our patient. This may indicate that ultrasonography surveillance of thyroid lymphoma should be carried out early.

Ultrasonography is often the first-line investigation with the presence of enhanced posterior echoes suggestive of PTL but biopsy is necessary for definitive diagnosis. Previously, open surgical biopsy was deemed necessary to differentiate thyroid lymphoma from thyroiditis and anaplastic carcinoma.¹¹ Recent studies have shown improvement in the accuracy of FNA when combined with immunophenotyping¹² with DLBCL being suspected from the high density of large monotonous to pleomorphic lymphoid cells and decreased or absent colloid. However, core-needle or surgical biopsies still have a role in distinguishing thyroiditis from low-grade MALT lymphoma and in ensuring that aggressive histologies such as mixed MALT lymphoma and DLBCL are not missed. In our patient, both fine-needle aspiration cytology and Tru-cut biopsy failed to give a definitive diagnosis and an open surgical biopsy was arranged to establish a proper histological diagnosis and to assess the status of the involved lymph node.

Stage IE and IIE thyroid non-Hodgkin's lymphoma have traditionally been treated with surgical resection but due to the aggressive nature and likelihood for systemic recurrence, both chemotherapy and radiotherapy are now recommended for patients with DLBCL with surgery often reserved for tissue diagnosis and relief of airway compression. Matsuzuka *et al*¹³ reported the use of CHOP plus radiotherapy in 119 patients with PTL and reported a survival rate of 100% at 8 years while Derringer *et al*³ found disease specific 5-year survival rates for DLBCL to be 71%. Addition of rituximab to the chemotherapy

regime further improved overall survival and is now the recommended chemotherapy regime in the treatment of PTL.

In summary, there needs to be a heightened index of suspicion for PTL in patients with HT who present with an enlarging neck mass. Timely diagnosis, especially where the histology is that of DLBCL can allow for earlier treatment with improved outcomes.

Learning points

- Increased index of suspicion for primary thyroid lymphomas (PTL) in patients with Hashimoto's thyroiditis (HT) and an enlarging neck mass. PTL, although rare, has a 60-fold risk in patients with HT.
- It is important for periodical ultrasound screening of patients with HT in order to detect lymphoma development early.
- Radiological imaging is helpful but only serves as an adjunct to the diagnosis of PTL; histological diagnosis is still needed for definitive diagnosis.
- Prognosis of PTL is good with relatively high survival rates of after chemoradiotherapy.

Contributors BC and CJS were involved in conception and design of study. BC, SC and CJS took part in acquisition of data. BC, SC and CJS analysed and interpreted the data. BC drafted the manuscript. SC and CJS revised the manuscript for critically important intellectual content. BC, SC and CJS approved the final version of the manuscript to be published.

Competing interests None declared.

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