Primary thyroid lymphoma with elevated free thyroxine level

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ABSTRACT

Primary thyroid lymphoma (PTL) is a rare form of thyroid cancer that is known to be associated with Hashimoto thyroiditis. This association is supported by the presence of elevated titres of both antithyroglobulin and antimicrosomal antibodies in up to 95 percent of patients with PTL. Most patients with PTL present with a rapidly enlarging neck mass and compressive symptoms. The majority of thyroid cancer patients have normal levels of thyroid hormones; they are rarely hyperthyroid, with no obvious clinical features of thyrotoxicosis. We describe a patient who presented with minimal clinical features of thyrotoxicosis despite having markedly elevated serum free thyroxine and suppressed serum thyroid-stimulating hormone levels.

Keywords: elevated free thyroxine hormone, Hashimoto thyroiditis, primary thyroid lymphoma, thyroid cancer, thyrotoxicosis

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INTRODUCTION

Thyroid cancer is the most common malignant endocrine tumour. However, it constitutes only about 1% of all malignancies. It is the differential diagnosis of a thyroid mass, which usually presents as a unilateral painless thyroid nodule in an otherwise asymptomatic patient.[1] Primary thyroid lymphoma (PTL) is a rare form of malignant thyroid cancer that is known to be associated with Hashimoto thyroiditis.[2] In contrast to the usual presentation of a benign thyroid swelling, patients with PTL are more likely to present with a rapidly enlarging neck mass that is frequently associated with compressive symptoms.[2]

Although most patients with thyroid cancers are euthyroid, some may present with elevated serum thyroxine levels with obvious clinical features of thyrotoxicosis.[3,4] We report a case of primary thyroid lymphoma with markedly elevated serum free thyroxine levels but minimal clinical features of thyrotoxicosis.

Table 1 Results of blood investigation.

Test	Level (reference range)
TWBC (x 10^9/L)	9.6 (4–11)
Haemoglobin (g/L)	15.8 (13–18)
Platelet (x 10^9/L)	428 (150–400)
Urea (mmol/L)	9.6 (4–8)
Potassium (mmol/L)	4.6 (3.5–5)
Sodium (mmol/L)	133 (135–145)
Creatinine (μmol/L)	132 (80–130)

TWBC: total white blood cell

CASE REPORT

A 69-year-old Malay man presented with a history of a slowly enlarging anterior neck mass for the past 20 years. However, about one month prior to admission, the patient noted a rapid increase in the size of the swelling, which associated with difficulty in swallowing and hoarseness of voice. There were no obvious symptoms of thyrotoxicosis except for recent weight loss, which was attributed to poor appetite over a period of four months prior to admission. The patient was also hypertensive but was not on regular medication.

On examination, the patient was fully conscious and orientated, and had a hoarse voice. His height and weight was 165 cm and 70 kg respectively. His blood pressure was normal at 120/80 mmHg and pulse rate was regular at 78 beats per minute (bpm). Clinically, there was no evidence of cardiomegaly, and examination of his respiratory system showed no abnormality except for right trachea deviation. His liver and spleen were not palpable, but his thyroid gland was enlarged (World Health Organization Grade 2).[5] It was nodular and firm but non-tender, with no bruit. Except for a firm, non-tender, solitary 2 cm × 2 cm lymph node in the left occipital area, no other lymphadenopathy was detected in the neck, supraclavicular, axillary or inguinal area. More importantly, signs of thyrotoxicosis, including tremor, hyperreflexia and proximal myopathy, were absent. Signs of Grave's disease such as exophthalmos, thyroid acropachy or pretibial myxoedema were also absent.

Table I shows the results of the blood tests taken on admission. Electrocardiography revealed sinus rhythm, with a rate of 76 bpm; Q wave was present in leads III

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Table II Preoperative thyroid function and thyroid autoantibody levels.

Hormone	Normal range	9 days pre-operation	3 days pre-operation
TSH (mIU/L)	0.3–4.2	0.1	0.2
FT4 (pmol/L)	12–22	37.8	31.7
Antithyroglobulin (IU/ml)	≤ 115	< 10	NR
Antithyroid peroxidase (IU/ml)	≤ 34	19	NR

TSH: thyroid-stimulating hormone; FT4: serum free T4; NR: not repeated

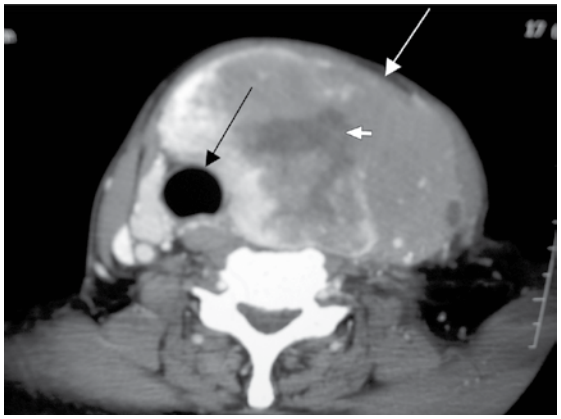

Fig. 1 Contrast-enhanced axial CT image of the patient's thyroid gland shows a heterogeneously enhancing thyroid gland (white arrow) with an area of necrosis (white arrow head) and the trachea pushed to the right (black arrow).

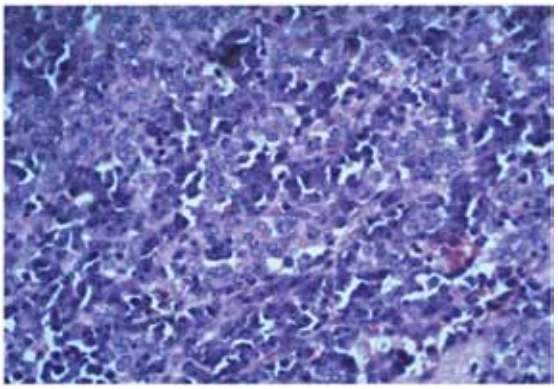

Fig. 2 Photomicrograph shows intense infiltration of the thyroid, with lymphoid cells that are difficult to differentiate from follicular cells (Haemotoxylin & eosin, × 400).

and avF, and T inversion was present in II, III, avF, V5–V6, which were suggestive of ischaemic heart disease (IHD). Chest radiography revealed a compressed trachea deviated to the right, with haziness of the superior mediastinum extending to the upper one-fifth of the sternum. The patient's heart size was normal, and his lung fields were clear bilaterally.

Fine needle aspiration cytology (FNAC) of the thyroid gland was performed twice. The first FNAC done on October 3, 2007 from the upper pole of right lobe showed a heterogeneous population of predominantly small, round lymphocytes with plasma cells, immunoblasts and large lymphocytes. A few Hürthle cells were also present. This was reported as 'compatible with chronic thyroiditis'. A second FNAC done on October 18, 2007 from the middle of the left lobe showed scanty lymphoid component that was mixed with peripheral blood, and was reported as 'no malignant cells seen'. Computed tomography (CT) of the neck and thorax on October 17, 2007 showed a large, well-defined, heterogeneously enhancing mass arising from the left thyroid lobe, measuring 7.1 cm × 11.2 cm × 14.0 cm. There were areas of necrosis within the mass, but no calcification was noted. There was also evidence of destruction of the adjacent hyoid bone and thyroid cartilage. Multiple nodes with an average size of about 1.5 cm were seen in the submental, left pharyngeal, paratracheal and precarinal areas, in the left carotid sheath and axilla bilaterally as well as in the anterior mediastinum. Multiple nodules were also noted in both apical lung fields. These features were suggestive of left thyroid carcinoma with lung metastases (Fig. 1).

Preoperative thyroid function test showed an elevated serum free T4 (FT4) level of 37.8 pmol/L and a low serum thyroid-stimulating hormone (TSH) level of 0.1 mIU/L, while thyroid autoantibodies were not raised (Table II). A presumptive diagnosis of left thyroid cancer with lung metastases was made. Debulking surgery was performed to relieve the compressive symptoms. On October 31, 2007, the patient underwent left thyroid lobectomy and isthmusectomy through a median sternotomy, followed by tracheostomy. As a precaution for the persistently raised serum FT4 levels, he was treated with propylthiouracil 200 mg tds, propranolol 40 mg tds and potassium iodide solution 41.5 mg (five drops) qid from five days preoperatively. Operative findings revealed a left thyroid tumour, firm-to-hard in consistency, and measuring 12 cm × 8 cm. The tumour extended superiorly to the left sternohyoid muscle, posteriorly to involve the left prevertebral fascia, medially into the tracheooesoghageal groove, and laterally to encase the left common carotid artery, causing left internal jugular vein thrombosis,

Table III Postoperative thyroid function test results.

Type of test	Day 1	Day 4	Day 11	Day 13	Day 18
TSH (mIU/L)	0.05	0.6	0.05	3.4	5.2
FT4 (pmol/L)	21.5	11.6	21.2	15.4	17.8

TSH: thyroid-stimulating hormone; FT4: serum free T4

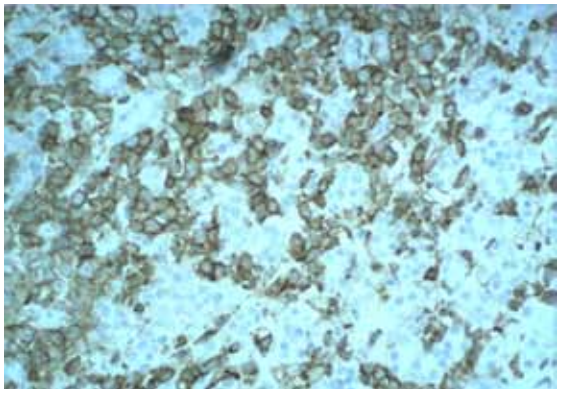

Fig. 3 Photomicrograph shows lymphoid cells with cytoplasmic membrane positivity (brown) against the pale unstained follicular epithelial cells with blue nuclei lying in between (Immunohistochemical staining for LCA, × 400).

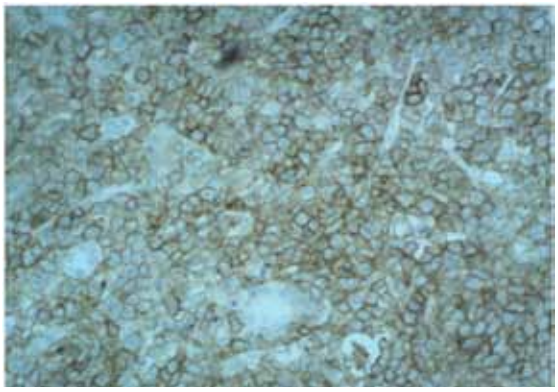

Fig. 4 Photomicrograph shows a majority of lymphoid cells staining positive for L26, a B-cell marker (Immunohistochemical stain, × 400).

inferiorly encasing the left brachiocephalic vein and the upper part of the pleura, and anteriorly invading the left omohyoid and sternohyoid muscles and the lower one-third of the left sternocleidomastoid muscle.

Histologically, a section from the left thyroid showed diffuse proliferation of malignant lymphoid cells replacing almost all of the thyroid follicles. These lymphoid cells had large vesicular nuclei with single to multiple nucleoli and scant to moderate amount of cytoplasm. Plasmacytoid and lymphoplasma cells were observed to be intermingled with these large cells. Mitosis was brisk (35/high power field). The residual thyroid follicles showed atrophic changes. Sections from the mediastinal lymph nodes showed infiltration of lymphoma cells (Figs. 2–4). The histology was reported as diffuse large B-cell immunoblastic lymphoma affecting the left thyroid lobe, with mediastinal node metastases.

The early postoperative period was uneventful, apart from a few episodes of paroxysmal atrial fibrillation (without haemodynamic instability), which were attributed to IHD (serum free thyroxine level had normalised immediately post operation), and controlled with oral digoxin. Antithyroid therapy was stopped on Day 3 post surgery, as the patient was clinically and biochemically euthyroid (Table III). On Day 7 post surgery, he suddenly experienced a cardiac arrest following an episode of acute coronary syndrome, and was actively resuscitated for 45 minutes. He subsequently developed hypoxic encephalopathy. His progress was further complicated by frequent paroxysmal atrial fibrillation, ventilator-associated pneumonia (trachea aspirate grew multiresistant *Acinetobacter* spp.) and septicaemic shock. Chemotherapy and radiotherapy were not initiated in view of his poor prognosis. The patient's family requested for discharge. The family's wish was respected, and he was discharged one month after the operation.

DISCUSSION

Over 90% of thyroid cancers are of the follicular or papillary variant, and are usually referred to as differentiated thyroid cancer. Rarer forms of thyroid cancer include medullary thyroid cancer arising from parafollicular C-cells, anaplastic carcinoma and Hürthle cell carcinoma.[1] PTL is a rare type of thyroid cancer, comprising approximately 1%–5% of all thyroid malignancies,[6,7] with an estimated annual incidence of 2.1 per million. PTL is 3–4 times more common in women than men, with the peak incidence at about 60 years of age.[6,7] Our patient was atypical, as he was male and older.

Many thyroid malignancies arise in essentially normal thyroid tissue and develop slowly.[8] The PTL in our patient had likely developed in a pre-existing multinodular goitre, as he had a thyroid swelling for over 20 years before the recent rapid enlargement. Hashimoto thyroiditis was noted in more than 90% of reported

cases of PTL. Patients with Hashimoto thyroiditis have an estimated 70%–80% risk of developing PTL.[7] The presence of elevated titres of both antithyroglobulin and antimicrosomal antibodies in up to 95% of patients with PTL further supports this association. It is possible that chronic antigenic stimulation in thyroiditis predisposes patients to neoplastic transformation.[7] In our patient, the finding of chronic thyroiditis from the patient's first FNAC of the thyroid gland supported the diagnosis of Hashimoto thyroiditis. The fact that his thyroid antibodies were not elevated was an uncharacteristic feature of Hashimoto thyroiditis. The diagnosis of thyroid cancer was made in this patient although both FNACs did not show evidence of cancer; he presented with symptoms of recent rapid enlargement of a chronic multinodular goitre, with CT of the neck and thorax showing evidence of thyroid carcinoma with lung metastases. Although the role of FNAC in diagnosing thyroid lymphoma has improved in recent years with the advent of immunophenotypic analyses such as flow cytometry and immunohistochemistry,[9] the procedure is operator-dependent, while the interpretation of FNAC relies on the availability of an expert cytopathologist. The absence of obvious generalised lymphadenopathy or hepatosplenomegaly in our patient, combined with histological description and staining characteristics of the tumour from surgical specimen, are compatible with the diagnosis of a lymphoma arising from the thyroid gland.

Most thyroid cancers occur in euthyroid individuals. However, some may have elevated serum free thyroxine levels at presentation, with or without clinical features of thyrotoxicosis. This can occur when there is concurrent Grave's disease, solitary toxic adenoma or toxic multinodular goitre. It is estimated that 1%–9% of patients with Grave's disease may develop thyroid cancer.[10] Another situation where a patient may present with hyperthyroidism is when there is widespread metastatic, functional thyroid cancer, which is most frequently observed with follicular cancer.[10-12] A more common cause of elevated serum free thyroxine levels, as in our patient, is the destruction of thyroid follicles by infiltrating tumour cells, resulting in a release of preformed thyroid hormones into the circulation.[3,4,13] The persistently elevated serum free thyroxine levels lead to TSH suppression.

It is interesting to note that our patient lacked overt features of thyrotoxicosis except for recent weight loss, which could also be attributed to decreased food intake due to poor appetite for the four months prior to presentation. It is possible that the serum FT4 elevation occurred only for a brief period of time, and hence, there was limited time for symptoms to develop.[4] It is also likely that the majority of released preformed thyroid hormone was in the form of thyroxine (T4). The absence of overt thyrotoxic features observed in this patient could be explained by the presence of this less active form of thyroid hormone.[14] Unfortunately, the serum triiodothyronine (T3) level was not available to support this explanation.

In conclusion, we report a case of primary thyroid lymphoma with biochemical evidence of hyperthyroidism, but without obvious signs and symptoms of thyrotoxicosis. The lack of thyrotoxic features is attributed to the release of functionally less active thyroid hormone thyroxine into the circulation due to follicular destruction by tumour cells.

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