CASE REPORT

A rare cause of hyperthyroidism: functioning thyroid metastases

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SUMMARY

Hyperthyroidism is a common medical problem that is readily treated with antithyroid medications. However, attributing the correct aetiology of hyperthyroidism alters management and outcome. We present a case of a 66-year-old woman with a seemingly common problem of hyperthyroidism associated with a goitre, which was initially attributed to a toxic nodule. However, Tc-99m pertechnetate uptake scan and thyroid-stimulating hormone receptor antibody were negative, inconsistent with a toxic nodule or Grave's disease. Her thyroid function tests proved difficult to control over the next few months. She eventually proceeded to a total thyroidectomy and histology revealed follicular variant papillary thyroid carcinoma. She was started on levothyroxine postoperatively but developed severe hyperthyroidism, revealing the cause of hyperthyroidism to be autonomously functioning thyroid metastases. Although functioning thyroid metastases are very rare, they need to be considered among the differential diagnoses of hyperthyroidism, as there are nuances in management that could alter the eventual outcome.

BACKGROUND

Hyperthyroidism is a very common condition that many general physicians will come across in their careers. However, functioning thyroid metastases is a very rare cause of hyperthyroidism; fewer than 100 case reports have been published since its first description in 1946. We describe a woman who had autonomously functioning thyroid metastasis from a follicular variant papillary thyroid carcinoma (PTC). The benefit of retrospection and greater awareness of this condition would perhaps have changed the outcome in this patient. We also highlight the nuances in management of this condition. It is for these reasons that we would like to bring this exceedingly rare condition to the attention of a wider readership.

CASE PRESENTATION

A 66-year-old Malay woman presented with a 6-week history of weight loss, tremors and heat intolerance. She developed palpitations, precipitating her admission into hospital and was found to be in fast atrial fibrillation. She was clinically hyperthyroid and had a firm large thyroid nodule in the left lobe. She had not noticed any recent change in the nodule size. There was no significant family history.

INVESTIGATIONS

Thyroid function tests (TFTs) confirmed hyperthyroidism: free T4 (fT4) 37.9 (9.6–19.1) pmol/L, fT3

25.1 (5–8.9) pmol/L, thyroid stimulating hormone (TSH) <0.006 (0.036–3.24) µ/L. Thyroglobulin antibody (TgAb) was positive 1221 (0–60) µ/L but TSH-receptor and thyroid peroxidase antibodies were both negative (0.4 (0–1.5) iu/L and 0 (0–60) µ/mL, respectively). The patient was started on carbimazole and propranolol. Given the negative TSH-receptor antibody (TRAb), a Tc-99m pertechnetate uptake scan was performed. Surprisingly, this showed diffuse reduction in tracer uptake throughout the thyroid gland, not supporting a diagnosis of toxic nodular disease.

A thyroid ultrasound scan revealed a large solid nodule in the left thyroid lobe measuring 5.2×4.9×3.3 cm with associated subcentimetre lymph nodes in the left upper neck. Fine-needle aspiration showed thyroid follicular cells arranged in microfollicles, but no malignant cells were seen. Lymph node cytology revealed only lymphoid cells, leading to a pathological diagnosis of a simple nodular goitre with reactive lymphoid hyperplasia. However, given the size of the nodule and the presence of sinister features on the ultrasound scan (figure 1A, B, ill-defined borders and microcalcifications), total thyroidectomy was recommended.

TREATMENT

The surgery was delayed over the next few months as the patient's thyroid function proved difficult to control (table 1).

There was an unpredictable response to antithyroid medications; small doses rapidly resulted in hypothyroidism while withdrawing treatment resulted in hyperthyroidism. The patient subsequently experienced persistent lower back pain following a fall. An MRI revealed large soft tissue masses in the sacrum and vertebrae, suggestive of metastatic bony deposits. A CT scan confirmed a large heterogeneous mass in the left thyroid gland, another mass centred on the sternum, the left iliac crest and upper sacrum and two lung nodules. The working diagnosis at this point was metastatic thyroid carcinoma. She was admitted to control her thyroid function (fT4 50.4 pmol/L at 11 months, see table 1) using carbimazole, Lugol's iodine, atenolol and steroids. TFTs presurgery was satisfactory (fT4 12.4 pmol/L, fT3 4.4 pmol/L, TSH <0.006 µ/L). A total thyroidectomy was performed, and histology revealed follicular variant PTC with areas of vascular invasion.

OUTCOME AND FOLLOW-UP

A day postsurgery, fT4 was 12.2 pmol/L. Antithyroid medications were stopped and 75 µg of levothyroxine was started. A week later, the

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Figure 1 (A) Large heterogeneous nodule with internal calcification and ill-defined borders. (B) Lymph node at level II, hilum present.

patient developed tachycardia, fever, drowsiness and fast atrial fibrillation. Repeat TFTs showed severe hyperthyroidism: fT4 69.3 pmol/L, fT3 24.2 pmol/L and TSH 0.103 μ L. A repeat TRAb was negative (0.4 IU/L), confirming that

hyperthyroidism was related to the large bulk of autonomously functioning thyroid metastatic tissue. Unfortunately, despite treatment for thyroid storm, she continued to deteriorate and passed away 12 days after thyroidectomy.

Table 1 Carbimazole dose in response to TFTs

	0 month	1 month	2 months	5 months	6 months	8 months	9 months	11 months
Free T4 (9.6–19.1 pmol/L)	37.9	7.6	2.4	4.6	28.9	1.6	8.9	50.4
TSH (0.36–3.24 mU/L)	<0.006	<0.006	1.62	1.59	<0.006	24.1	0.019	<0.006
Carbimazole prescribed in response to TFTs	30 mg	5 mg	2.5 mg	None	10 mg	None	None	See text

TFTs, Thyroid function tests; TSH, thyroid-stimulating hormone.

DISCUSSION

Thyrotoxicosis is seldom associated with thyroid carcinoma, the most common observation being an incidental papillary microcarcinoma discovered on histopathology in patients who have undergone thyroidectomies for Grave's disease or toxic multinodular goitre.¹ Very rarely, thyrotoxicosis occurring in differentiated thyroid cancer is due to autonomously functioning metastases; the first report was by Leiter *et al*² in 1946. Since then, fewer than 100 cases have been reported.³ The majority had follicular carcinoma with functioning metastases in the bone or lung at presentation but a few developed hyperthyroidism up to 15 years after the cancer diagnosis.^{3,4} Pure PTC with functioning metastases has been reported in only a handful of cases,^{5,6} one of which was a clear cell variant of PTC.⁷

Several features suggest functioning thyroid metastases in this patient: exclusion of hyperfunctioning thyroid gland, low iodine uptake into the thyroid and failure of thyrotoxicosis to resolve following thyroidectomy.⁸ The low thyroidal uptake using Tc-99m pertechnetate implied that metastases were present even at presentation. Another possibility could be that of concomitant thyroiditis due to cell-mediated thyroid injury given that the TgAb was positive. This is unlikely given the prolonged period of hyperthyroidism. In retrospect, performing a whole body ¹²³I scan would have distinguished between the two and detected metastases at presentation.

The aetiology of hyperthyroidism was likely related to autonomously functioning bulky metastases,⁹ given the absence of long-acting thyroid stimulators both at initial presentation as well as post-thyroidectomy. Adenomas and multinodular goitres that are toxic are the result of focal and/or diffuse hyperplasia of follicular cells of which the functional capacity is independent of TSH. Activating mutations in the TSH-receptor^{10,11} and Gs- α subunit¹⁰ have been found in these patients and perhaps may be the underlying mechanism in functioning metastases as well.

The unpredictable response to antithyroid medications has been previously noted. Massive metastatic or large primary follicular carcinomas have been noted to show a decrease in T4 levels and an increase in T3 and T3/T4 ratios, even in the absence of functioning tumours.¹² This may be related to increased type 1 and 2 iodothyronine deiodinase (D1 and D2), the activity levels of which have been found to be many times higher in tumour tissues from patients with T3 thyrotoxicosis.¹³ This could contribute to difficulties in predicting response to antithyroid medications if fT3 levels are not measured. Monitoring fT3 in patients on suppressive thyroxine therapy post-thyroidectomy is therefore important, since patients may experience hyperthyroid symptoms due to increased T3 levels despite lower T4 levels, necessitating decreased levothyroxine doses.¹³ For a similar reason, measurement of fT3 in addition to fT4 and TSH ought to be considered in those with massive metastatic follicular thyroid carcinoma under TSH-suppressive therapy, even if the metastases are known to be non-functioning.

Lastly, while most patients receiving ¹³¹I therapy ought to have TSH levels above an arbitrary level of >30 μ L to increase uptake, those with hyperfunctioning metastases can sequester large quantities of ¹³¹I even in the presence of suppressed TSH levels, potentially increasing the risk of a thyroid storm following radioiodine treatment.⁹ This is thought to be related to the release of thyroid hormone following tumour cell lysis and may be prevented by pretreatment with antithyroid drugs and steroids.⁹ Once free thyroid hormone levels normalise, recombinant human TSH may be needed to stimulate suppressed TSH levels and ensure optimal uptake.

To our knowledge, this is the first reported case of functioning thyroid metastases from follicular variant PTC. It is exceedingly rare but needs to be considered among the differential diagnoses, particularly when the cause of hyperthyroidism is unclear. fT3 levels should be monitored in light of increased deiodinase activity. Hyperthyroidism may be expected post total thyroidectomy and ought to be treated prior to radioiodine ablation.

Learning points

- Functioning thyroid metastases is exceedingly rare but needs to be considered among the differential diagnoses of hyperthyroidism.
- When neither the Tc-99m pertechnetate scan nor the thyroid-stimulating hormone receptor antibody reveal the cause of hyperthyroidism to be at the level of the thyroid gland, a whole body ¹²³I scan can be useful in detecting functioning thyroid tissue exogenous to the thyroid gland.
- In functioning thyroid metastases, free T3 levels should be monitored in titrating antithyroid medications.
- Hyperthyroidism is to be expected post total thyroidectomy and ought to be treated prior to radioiodine ablation.

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