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Case Report

Taken by Storm: Functional Metastases in Follicular Thyroid Carcinoma

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INTRODUCTION

Follicular thyroid carcinoma (FTC) is the second most common differentiated thyroid malignancy, after papillary thyroid carcinoma (PTC), and accounts for approximately 10%–20% of all thyroid cancers.(1) It is more common in women and in older individuals, usually presenting in the fifth and sixth decades of life. Risk factors for FTC include a history of radiation exposure during childhood and a family history of thyroid malignancy.(2) Patients may initially present with a thyroid nodule (with or without extrathyroidal extension) or with metastatic disease. Spread is typically haematogenous with distant metastases occurring in 10%–15% of patients with FTC.(2) FTC is often associated with a more aggressive course, distant metastases and a higher mortality rate than PTC. The long-term survival rates range from 31–43% in the presence of metastatic disease.(2)

FTC commonly metastasizes to bone and lung, with bony metastases usually presenting as lytic lesions. Less common sites include the brain, liver, bladder and skin. Functioning thyroid metastases in FTC are a rare cause of hyperthyroidism with fewer than 100 cases reported. Almost all cases reported have had extensive metastatic disease to bone, with or without spread to other organs. We describe a patient who presented with autonomously functioning metastases from FTC more than 25 years post-total thyroidectomy.

CASE REPORT

A 71-year-old African female presented to the orthopaedic clinic with left hip and back pain. She had undergone a total thyroidectomy in 1992 and was on levothyroxine replacement therapy. Her medical records could not be traced as the patient had been lost to follow-up. She was compliant on thyroid hormone replacement therapy.

A T2-weighted MRI of the spine demonstrated an ill-defined hyperintense, expansile lesion in the right iliac blade involving the sacro-iliac joint and the lateral sacral alae. There was destruction of cortical bone and extensive surrounding oedema suggestive of metastatic disease in the sacrum. Skeletal scintigraphy showed a large soft tissue mass occupying most of the right hemi-pelvis with extensive erosions and lytic changes in right iliac blade, sacrum, right superior and inferior pubic rami, right and left ischium (Figure 1A).

At initial presentation, the patient was clinically and biochemically euthyroid with a thyroid stimulating hormone (TSH) level of 2.35 mIU/L (0.27–4.20 mIU/L), a thyroxine (T4) level of 14.1 ng/dL (12–22 ng/dL) and a triiodothyronine (T3) level of 4.0 ng/dL (3.9–6.7 ng/dL). There was a markedly elevated thyroglobulin level of 5000 ng/ml (3.5–77.0 ng/ml) and a corrected calcium of 2.94 mmol/L (2.20–2.55 mmol/L). TSH receptor-stimulating antibody (TRAb) levels were not measured. She had no residual thyroid tissue on thyroid sonography.

Biopsy of the sacral lesion confirmed a diagnosis of metastatic FTC demonstrating lesional tissue with no representation of bony trabeculae or haematopoietic tissue (Figure 2A). The lesion comprised of well-formed colloid-containing thyroid follicles (Figure 2B), with the neoplastic cells having large, atypical nuclei. There were no nuclear features of PTC (Figure 2C).

The patient was assessed as having metastatic FTC. In view of the extensive bony metastases, she was offered radioactive iodine ablation (RAI). Prior to RAI, her thyroid hormone replacement therapy was discontinued and the hypercalcaemia was managed with intravenous fluids and zoledronic acid. She was re-admitted 3 months later with a pathological fracture of the right hip. Despite being off all thyroid hormone replacement therapy, she was biochemically hyperthyroid with a disproportionately elevated T3 level of 49.9 pmol/L.

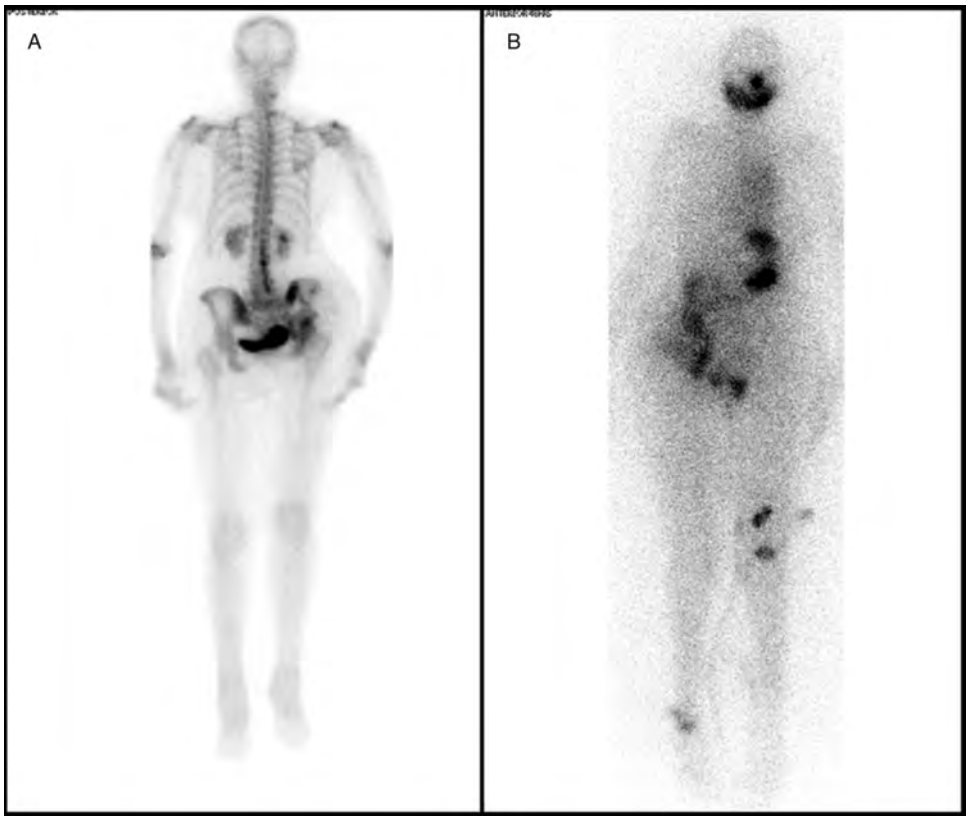

Fig 1: (A) Skeletal scintigraphy using technetium-99 showing a large soft tissue mass occupying most of the right hemi-pelvis with extensive erosions and lytic changes in right iliac blade, sacrum, right side superior and inferior pubic rami, right & left ischium. (B) Diagnostic whole-body thyroid scintigraphy using I^{131} revealed extensive uptake in both lungs (with predominant uptake on the right), a soft tissue mass at T8/9, right hemi-pelvis involving the iliac bone, ischium extending to the L5 vertebra, acetabulum and proximal femur, and left inferior ramus.

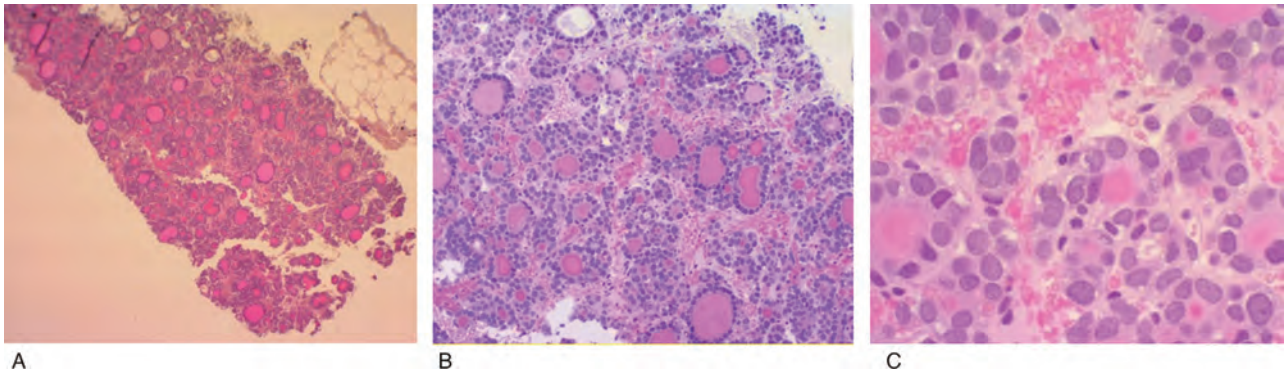

Fig 2: Histology of the sacral lesion. (A) Low power view of tissue core (40×); (B) Thyroid follicles with dense colloid (100×); and (C) High power view (400×). The sections represent entirely lesional tissue. The neoplastic tissue consists of thyroid glands proliferating in well-formed colloid containing follicles and infiltrative trabeculae in areas. The neoplastic cells have atypical, large nuclei. There are no nuclear features of a papillary thyroid carcinoma. There is no representation of bony trabeculae or haematopoietic tissue.

The patient was put into traction and an arterial embolization of the tumour mass was performed. She subsequently developed a nosocomial chest infection. The patient's clinical condition deteriorated and she developed clinical features of hyperthyroidism. An assessment of a thyroid storm was made based on a Burch–Wartofsky score of 80.(3) She was treated with maximal doses of anti-thyroid therapy (carbimazole), corticosteroids, beta-blockade and

intravenous antibiotics. Administration of Lugol's iodine was deferred in anticipation of a diagnostic thyroid uptake scan using I^{131}.

After days of therapy, the patient improved. Diagnostic whole-body thyroid scintigraphy revealed uptake in both lungs, T8/9 verterbra, right hemi-pelvis involving the iliac bone, ischium extending to the L5 vertebra, acetabulum and proximal femur, and left inferior ramus (Figure 1B). There was no evidence of residual thyroid tissue in the thyroid bed. Given the extent of her disease, a decision was made with the patient to opt for palliation. The patient succumbed shortly thereafter.

DISCUSSION

Thyroid carcinoma leading to thyrotoxicosis is a rare, but well-described phenomenon. It occurs more commonly in metastatic FTC than PTC.(4) The origin of the metastatic disease in this patient was unproven owing to missing records, but it is probable that the reason for her thyroidectomy was FTC. Certain features supported the diagnosis of functional thyroid metastases namely hyperthyroidism in the absence of any residual thyroid tissue on ultrasonography, the absence of thyroid RAI uptake and an increased RAI uptake by metastatic lesions.

Most cases of FTC with functioning metastases present at the outset.(5) A minority of patients develop hyperthyroidism up to 15 years after their initial diagnosis with only a few cases reported beyond two decades of initial presentation.(5,6) There are no reports, to our knowledge, of functional metastatic FTC in a patient of African descent.

Thyrotoxicosis is seldom associated with a thyroid malignancy as thyroid carcinomas are typically less efficient in concentrating iodine and producing thyroid hormone than normal thyroid tissue.(4) The most commonly observed scenario is that of an incidental papillary micro-carcinoma being discovered on histopathology in a patient who has undergone thyroidectomy for Graves' disease or a toxic multinodular goitre.(7,8) Nearly all patients with functional thyroid carcinoma and symptomatic hyperthyroidism have widely metastatic FTC.(9)

The precise mechanism of thyrotoxicosis by thyroid cancer metastasis is unknown. It is thought that a large aggregate tumour bulk may produce enough thyroid hormone to induce hyperthyroidism.(8) In addition, cases with TSH receptor autoantibodies have been reported, which would potentially increase the synthesis of thyroid hormone by the tumour.(10) Most patients with functional FTC present with T3-toxicosis. The mechanism here is thought to be related to increased type 1 and type 2 iodothyronine deiodinase activity in tumour tissue.(8,10) In this patient, we propose that both the extensive bulky metastatic disease and subsequent deiodination from T4 to T3 as reasons for hyperthyroidism.

The reason for a normal TSH level despite markedly elevated T3 levels is unexplained. We hypothesise that the relatively short duration of systemic thyrotoxicosis may have been of too short a time span to allow sufficient negative feedback to suppress TSH. In addition, there may be some resistance to TSH suppression due to the likely persistent effects of thyrotropin-releasing hormone (TRH). Suppression of prepro-TRH mRNA requires T4 in circulation to be taken up by astrocytes and tanycytes by the organic anion-transporting polypeptide (OATP) and monocarboxylate transporter 8 (MCT8) thyroid hormone transporters and then undergo 5′-deiodination in these cells to form T3. In essence, T4 is required for suppression of TRH via OATP and MCT8. In this patient, the deficiency of T4 may have resulted in failure to suppress TRH and hence delayed suppression of TSH.

The administration of radio-contrast medium during arterial embolization with a resultant Jod-Basedow phenomenon; the release of T3 from the tumour into circulation post-embolization; combined with a nosocomial infection are the most likely precipitants for the thyroid storm. To our knowledge, only a few cases of thyroid storm in association with functional thyroid cancer have been described.

FTC is typically associated with a poorer prognosis than PTC.(2) Other poor prognostic factors include the presence of metastatic disease and increased tumour size. The poor prognosis in this case was likely related to the patient's age, extensive metastatic disease and delayed intervention owing to the very late presentation following thyroidectomy.

CONCLUSION

We describe a 71-year-old patient who presented with T3-thyrotoxicosis as a result of functional metastatic FTC more than 25 years post-total thyroidectomy. Functional thyroid carcinoma is a rare, but well-described phenomenon and must be considered when evaluating thyroid carcinoma with concurrent hyperthyroidism.

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