CASE REPORT

Primary tuberculosis of the thyroid gland: an unexpected cause of thyrotoxicosis

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SUMMARY

We describe a 38-year-old Indian man who presented with a 2-week history of fever, night sweats and neck swelling who was found to be clinically thyrotoxic with a nodular goitre, tachycardia and high fever. Biochemical investigation revealed hyperthyroidism in association with deranged liver function tests and raised inflammatory markers. Ultrasound and CT scans of the neck revealed multinodular thyroid enlargement. He was considered most likely to have an acute infectious thyroiditis with a differential diagnosis of a toxic multinodular goitre and was started on carbimazole and antibiotics. He underwent fine needle aspiration of the thyroid which revealed necrotic cells and acid-fast bacilli, confirming a diagnosis of primary tuberculosis (TB) of the thyroid gland with no evidence of any other organ involvement on systemic imaging. He was started on TB therapy for 6 months and discharged with outpatient follow-up. Symptoms and biochemical markers subsequently resolved.

BACKGROUND

Primary tuberculosis (TB) of the thyroid gland is extremely unusual and may have a number of different clinical manifestations. It usually mimics more common conditions such as thyroid adenoma or carcinoma, lymphoma, infective or granulomatous thyroiditis, Graves' disease, multinodular goitre or bacterial abscess. This delays diagnosis especially if there is no evidence of other organ involvement. There are very few cases where hormone abnormalities have been observed but as demonstrated in this case, TB may be a cause of thyrotoxicosis mimicking Graves' disease or an infective thyroiditis in the absence of pulmonary or other organ involvement. We suggest, therefore that TB should feature on the differential diagnosis of thyroid disease especially in patients from countries where TB prevalence is high or in patients who have a history of TB or TB contact.

CASE PRESENTATION

A 38-year-old Indian man presented to the emergency department with a 2-week history of fever, drenching night sweats, a dry cough and neck swelling. He had been treated with two courses of amoxicillin with no symptomatic improvement. He had no medical history of note and was not taking any regular medication. He did not recall any previous exposure to TB and denied any foreign travel since he moved to the UK 6 years previously. He was a smoker of 10 pack-years. He had visited the general practitioner who had requested routine

blood tests including a thyroid profile which had revealed a high T4.

On admission he was febrile with a temperature of 40°C and tachycardic with a heart rate of 155 bpm. Clinical examination revealed a mildly tender, enlarged nodular thyroid gland. He had a fine tremor of the hands. Cardiovascular, respiratory and abdominal examinations were otherwise unremarkable and he had no cervical, axillary or inguinal lymphadenopathy.

INVESTIGATIONS

ECG showed sinus tachycardia with no ischaemic features or arrhythmia.

Haematological investigation revealed normal haemoglobin level but a raised white cell count ($12.4 \times 10^9/L$) with neutrophilia. Liver function tests were deranged with alkaline phosphatase 161 IU/L, alanine aminotransferase 156 IU/L and bilirubin 16 mmol/L. Thyroid function tests performed the previous week revealed a low thyroid stimulating hormone (TSH, 0.14 mIU/L) and high free T4 (25.1 ng/dL) confirming hyperthyroidism. On admission his T4 level had increased to 69.5 ng/dL. Thyroid autoantibody screen was negative. Erythrocyte sedimentation rate (ESR) was 43 mm/h and C reactive protein (CRP) was 373 mg/L.

Blood cultures and urine cultures were persistently negative as were his urinary legionella and pneumococcal antigen tests. HIV and viral hepatitis serology were negative.

Chest radiograph showed a soft tissue swelling in the neck but no lung field abnormalities.

He underwent an ultrasound of his neck which showed enlargement of both lobes of the thyroid and isthmus with a non-homogenous echo pattern and multiple heterogenous nodules with cystic degeneration. A large heterogenous nodule was visualised in the left lobe with cystic and solid areas but no increased vascularity. There were multiple reactive lymph nodes in the neck. The appearances were considered most likely to represent a hyperplastic multinodular goitre.

CT of the chest abdomen and pelvis confirmed marked thyroid enlargement with multiple nodules, the largest of which was in the left lobe measuring 5 cm with cystic necrosis but no retrosternal extension (figure 1). There were no pulmonary lesions, or significant lymph node enlargement in the chest abdomen or pelvis and no solid organ pathology below the diaphragm.

He underwent thyroid scintigraphy using technetium-99m sodium pertechnetate (figure 2).

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Figure 1 CT of the thyroid gland showing thyroid enlargement and a large left sided nodule with cystic necrosis.

This showed a large photopenic area over the region of the left lobe of the thyroid with a small focus of uptake in its inferior aspect which was considered to be non-specific (possibly representing a functioning nodule, residual thyroid tissue or inflammation). There was no uptake in the rest of the thyroid.

The patient subsequently underwent fine needle aspiration (FNA) of the left thyroid nodule during which 10 mL of turbid fluid was aspirated. Samples were sent to microbiology for bacterial culture, acid-fast bacilli (AFB) staining and TB culture. The AFB staining was positive on three samples from the thyroid nodule and subsequent TB culture was positive, confirming a diagnosis of TB thyroiditis.

DIFFERENTIAL DIAGNOSIS

This patient's presentation has a number of differential diagnoses.

Thyroiditis due to inflammation of the thyroid gland can cause hyperthyroidism and shows low or no uptake on thyroid scintigraphy. It may be infectious due to viral or bacterial infection, silent (autoimmune) or granulomatous due to thyroid infiltration in conditions such as sarcoidosis. Bacterial thyroiditis is usually acute with rapid onset of symptoms as in this case. Subacute thyroiditis (such as De Quervain's thyroiditis) occurs over a longer time period and is usually attributed to viral infection. Infectious thyroiditis can cause hyperthyroidism and hypothyroidism and usually causes painful swelling of the thyroid gland in association with fevers as in this case. In infective and autoimmune thyroiditis an initial phase of hyperthyroidism is thought to be due to release of preformed thyroid hormone when follicles are damaged. This is often followed by a phase of

hypothyroidism and finally euthyroidism. In contrast to infective thyroiditis, silent thyroiditis is painless making infection the most likely aetiology in this case.

A toxic multinodular goitre presents with hyperthyroidism and a multinodular thyroid swelling as in the case described here. This is due to excess thyroid hormone production from functionally autonomous thyroid nodules. Thyroid scintigraphy, however, would be expected to show high uptake with multiple 'hot' nodules which are responsible for producing excess thyroxine. This contrasts with the case described here which showed only one small focus of uptake in the left lobe of the thyroid and no uptake elsewhere on thyroid scintigraphy.

Graves' disease is the most common cause of hyperthyroidism in the developed world. It is an autoimmune disease in which autoantibodies to the TSH receptor cause persistent stimulation. It can be associated with goitre as in this case and symptoms are of hyperthyroidism as described above. Thyroid scintigraphy, however, shows high uptake throughout the thyroid gland and the characteristic features of Graves' ophthalmopathy and pretibial myxoedema were not present in this patient.

Thyroid adenoma, carcinoma and lymphoma can present with thyroid enlargement. A functional adenoma may result in hyperthyroidism and would be expected to show a focus of high uptake on radioiodine or ^{99m}Tc sodium pertechnetate scan. Thyroid carcinoma or lymphoma usually show low (or nearly absent) uptake on thyroid uptake scans and do not typically cause hyperthyroidism (euthyroidism and hypothyroidism are much more common). The absence of systemic lymph node enlargement on CT makes lymphoma unlikely. All of these diagnoses would be expected to occur over a longer time period than this patient's symptoms.

TREATMENT

Initially, the patient was started on carbimazole in light of thyrotoxicosis and the possibility of a toxic multinodular goitre. This was subsequently stopped after thyroid scintigraphy which did not show significant uptake.

In light of persistently high temperatures, the raised white cell count and the very high CRP he was considered most likely to have an infective thyroiditis although other considerations were lymphoma and TB. He was started on empirical intravenous co-amoxiclav and clarithromycin to cover a bacterial infection on microbiology advice. His heart rate remained persistently raised so he was started on propranolol 40 mg twice per day.

Following the results of the FNA which confirmed a diagnosis of TB, the patient was started on TB treatment with quadruple therapy; Rifater (rifampicin 120 mg, isoniazid 50 mg, pyrazinamide 300 mg) six tablets daily and ethambutol 1 g daily for 2 months, after which he was planned for step down to dual therapy with rifampicin and isoniazid for a 4-month continuation phase pending the results of the resistance profile of TB cultures.

OUTCOME AND FOLLOW-UP

The patient was planned for a total of 6 months of treatment (2 months of quadruple therapy with possible step down to dual therapy for 4 months depending on the resistance profile) and was discharged with outpatient follow-up by the respiratory team and TB nurses. His liver function tests and thyroid function were closely monitored on discharge and he underwent visual testing having started ethambutol treatment which can cause optic neuritis and red-green colour blindness. His symptoms have resolved and thyroid function tests have returned to normal since starting TB treatment.

Figure 2 ^{99m}Tc Pertechnetate scintigraphy of the thyroid gland: (A) anterior and (B) anterior with sternal notch marker.

DISCUSSION

Mycobacterium tuberculosis (MTB) is an aerobic bacillus responsible for most cases of tuberculous infection. Approximately one-third of the world's population are estimated to be infected.¹ In 2012, 1.4 billion deaths were due to MTB which is the second largest cause of death due to an infectious disease after HIV.² The highest incidence is in Asia and Africa with 40% of the world's cases occurring in India and China.³ Between 5% and 10% of people infected with MTB will develop symptoms within their lifetime (higher rates are seen in individuals coinfecting with HIV). TB usually affects the lungs (in 90%)⁴ but in 15–20% of cases it affects sites outside the lungs (extrapulmonary TB), most commonly lymph nodes.⁵ Other sites which may be affected include the bone and joints, pleura, the central nervous system (especially in immunocompromised individuals), peritoneum, the gastrointestinal or genitourinary tracts and the pericardium.⁵ Organs such as the heart, thyroid and pancreas and tissues such as striated muscle are relatively resistant to TB infection.

Primary TB of the thyroid gland is an extremely rare extrapulmonary manifestation of TB even in areas where TB prevalence is very high.⁶ It has been estimated to occur at a frequency of 0.1–0.4% of all TB cases.⁷ This is highlighted in a study by Mondal and Patra⁶ who described only 18 cases of thyroid TB out of 1565 patients who underwent fine-needle aspiration cytology (FNAC) of thyroid lesions over 9 years, 4 of whom had known pulmonary TB.

The mechanisms underlying the relative resistance of the thyroid gland to TB infection are unknown. Factors such as the thyroid capsule, high iodine levels within the gland, bactericidal action of the colloid, antitubercular action of thyroid hormones and the abundant lymphatic and vascular supply to the thyroid gland may explain why primary TB at this site is seldom encountered.⁸ Thyroid status may also play a role; it has been suggested that in hyperthyroidism an increase in the physiological activity of phagocytes may result in destruction of the mycobacteria.⁸

Thyroid involvement more commonly occurs as part of disseminated spread in miliary TB⁹ or via direct extension from

cervical lymph nodes or the larynx. Less common presenting features include diffuse or nodular thyroid swelling, a discrete solid or cystic mass, other forms of thyroiditis or as an acute abscess.¹⁰ Patients are usually euthyroid but primary TB of the thyroid gland may cause thyrotoxicosis (possibly through autoimmune mechanisms)¹¹ or hypothyroidism (due to gland destruction),¹² although very few cases of hormone abnormalities have been described in the literature as thyroid synthetic function is rarely affected.¹³ The presentation is usually subacute (and may mimic a granulomatous thyroiditis such as de Quervain's) but may occur as an acute thyroiditis as in the case described above where symptoms developed over 2 weeks. Clues about the underlying aetiology include symptoms such as fevers, weight loss, night sweats and lymphadenopathy, although hyperthyroidism, viral thyroiditis and lymphoma could produce similar symptoms. The raised ESR and CRP were non-specific clues that the aetiology may be infective. Tuberculous thyroiditis commonly presents with localised pain which can mimic granulomatous and other infective forms of thyroiditis.¹⁴ If pain is absent it may be mistaken for malignancy.

Kapoor *et al*¹¹ described a similar case to ours in 1985; a female patient presenting with symptoms of hyperthyroidism who was found to have thyroid TB incidentally following subtotal thyroidectomy. In contrast to our case, their patient presented with a much longer history of a year and a half and did not have thyroid enlargement. Their case highlights the value of FNA or FNAC or biopsy of the thyroid gland in cases suspicious of TB to avoid unnecessary surgery. In contrast, Chaudhary *et al*¹² described a case of primary TB of the thyroid gland in association with hypothyroidism, while most other case reports in the literature describe patients who were clinically and biochemically euthyroid. These cases demonstrate how variable the presentation of TB can be in terms of symptoms and biochemical markers.

Patients who are suspected to have thyroid TB should have systemic imaging with a chest radiograph in the first instance and should undergo imaging of the neck using ultrasound and CT. These may reveal cervical lymphadenopathy and will

Figure 3 Flow diagram showing the differential diagnosis of thyrotoxicosis based on radionuclide uptake on thyroid scintigraphy.

identify the characteristics of the thyroid gland. Radiological features are non-specific although contrast-enhanced CT may identify a caseous necrotic lesion (dermal sign).¹⁵ Thyroid scintigraphy is useful to differentiate between thyroiditis and other forms of hyperthyroidism based on the uptake of radionuclide (figure 3). The preferred radiopharmaceutical agent is iodine-123 but technetium-99m sodium pertechnetate is a suitable alternative with lower radiation exposure. FNAC under ultrasound guidance and histopathological examination are the gold standard investigations¹⁶ with AFB staining and TB culture of pus or tissue in cases where the index of suspicion is high. The hallmark histological features are caseating epithelioid cell granulomas (which are specific for TB infection) and Langhans giant cells.¹⁷ Caseation distinguishes TB from other forms of granulomatous thyroiditis, for example, sarcoidosis.

Treatment with quadruple antituberculous therapy (rifampicin, isoniazid, pyrazinamide and ethambutol) has been shown to result in full resolution of thyroid TB in majority of cases,¹⁸ although adjunctive drainage of abscesses can be useful. It is therefore important to identify the correct diagnosis to avoid unnecessary surgery which may be performed when thyroid TB is mistaken for malignancy.¹⁹ The duration of treatment varies; the patient described here was treated for 6 months, although some advocate 9 months of treatment.¹⁰ Resolution is usually complete with medical treatment alone, although occasionally surgery or drainage are necessary adjuncts.

Fortunately our patient's diagnosis was confirmed soon after admission and he did not undergo any unnecessary invasive pro-

cedures. This case of primary TB of the thyroid gland was challenging to diagnose due to the rarity of the disease and the atypical presentation with acute onset of symptoms and lack of evidence of TB elsewhere. Furthermore, there have been very few reports of hormone abnormalities associated with thyroid TB in the literature, thus TB was an unexpected cause of thyrotoxicosis in this case.

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Learning points

- Primary tuberculosis (TB) of the thyroid gland is a very rare extrapulmonary manifestation of TB.
- Primary TB of the thyroid can mimic a number of more common diseases of the thyroid gland and can occasionally cause thyroid hormone abnormalities.
- TB should be included in the differential diagnosis of patients presenting with thyroid disease especially in those with prior contact with people infected with TB or those from high prevalence areas.
- Fine-needle aspiration cytology or biopsy with acid-fast bacilli staining and TB culture are the gold standard investigations for diagnosis.

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