Clinical Reports

‘Apathetic’ thyrotoxicosis presenting with hypercalcaemia and spurious normalization of serum thyroid hormone levels

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Summary: A patient with thyrotoxicosis presented with weight loss and hypercalcaemia, leading to an erroneous diagnosis of occult malignant disease. Intercurrent illness and drug treatment of hypercalcaemia in this patient caused a depression of circulating thyroid hormone levels, leading to a delay in diagnosis.

Radionuclide studies of thyroid function, in contrast, consistently suggested a thyrotoxic state. It is suggested that in this situation, radionuclide studies may give a more accurate assessment of thyroid status than biochemical tests, which may be difficult to interpret in the presence of non-thyroidal illness.

Introduction

In non-thyroidal illness, serum levels of thyroxine (T₄) and triiodothyronine (T₃) may fall, in association with normal or low levels of thyrotrophin (TSH) – the so-called euthyroid sick syndrome.^{1,2} While the biological significance of these changes is unclear,^{3,4} they may cause diagnostic confusion in the rare instances where true thyrotoxicosis and a severe non-thyroidal illness co-exist.^{5,6,7} In this report, we describe a patient with thyrotoxicosis in whom a profound fall in thyroid hormone levels occurred, due to a number of factors, leading to a delay in diagnosis.

Case history

A 60 year old woman was admitted for investigation of marked weight loss (25 kg), anorexia and malaise. Hypercalcaemia (adjusted calcium 3.15 mmol/l) had been discovered by her general practitioner, and the clinical suspicion of an occult malignant tumour was high. She was taking no medication other than clobazam for anxiety. On clinical examination she appeared unwell, had generalized muscle wasting and was dehydrated. Pulse was 96 beats/min, regular, and blood pressure 160/70 mm Hg. A smooth, soft goitre was palpable, but no other signs or symptoms of

thyrotoxicosis were elicited. Preliminary investigations were as follows; serum calcium 3.05 mmol/l (normal 2.20–2.60 mmol/l); serum phosphate 0.95 mmol/l (normal 0.70–1.40 mmol/l); serum albumin 30 g/l (normal 35–55 g/l); alkaline phosphatase 520 U/l, gamma glutamyl transferase (GGT) 90 U/l (normal < 35 U/l). Isoenzyme studies indicated that the elevation in alkaline phosphatase was largely due to an increase in the hepatic isoenzyme. Serum bilirubin, transaminases, urea, electrolytes and creatinine were normal and plasma parathyroid hormone was undetectable on two occasions. Haemoglobin was 10.9 g/dl, ESR 45 mm/h but sternal marrow aspirate and electrophoresis of blood and urine samples were normal. Other investigations performed in search of a malignant tumour included chest X-ray, bronchoscopy, abdominal ultrasound scan, barium meal and enema, radionuclide bone and liver scans, and radiological skeletal survey. All were normal.

The hypercalcaemia was initially treated by intravenous infusions of 0.9% sodium chloride solution 4 litres daily, combined with frusemide 80 mg daily, prednisolone 40 mg daily and salmon calcitonin 400 IU three times a day.

Shortly after admission to hospital, the patient developed right sided lower chest pain, cough and purulent spit and was treated for a presumed chest infection with oral ampicillin and erythromycin.

Figure 1 Clinical and biochemical details of the patient studied. CBZ = carbimazole therapy (45 mg/day); TRH = thyrotrophin releasing hormone test; ^{131}I = ablative radioactive iodine (^{131}I) therapy; Tc uptake = technetium-99m thyroid uptake test.

Serial thyroid function tests and other relevant clinical data are shown in Figure 1. While the first thyroid hormone measurements taken by the general practitioner were clearly within the thyrotoxic range, we were unaware of these results early in the patient's hospital admission. Nevertheless, a course of carbimazole was commenced on the basis of the elevated T_3 and T_4 levels on the day of admission, and the subsequent thyroid scan appearance. Propranolol was also given. Both drugs were stopped, however, when the results of three further thyroid function tests (two taken before carbimazole therapy) became available yielding normal values. Two subsequent thyrotrophin

releasing hormone (TRH) tests showed a consistently 'flat' response of TSH (all samples $<1 \text{ mU/l}$). On the basis of these, and the elevated $^{99\text{m}}\text{Tc}$ thyroid uptake (10.7%; normal $<3\%$) antithyroid drug therapy was resumed. This led to a marked improvement in the patient's clinical state, correction of hypercalcaemia and gain of weight. Carbimazole drugs were continued for 6 weeks and ^{131}I therapy was then given. The patient subsequently became hypothyroid but is now well and euthyroid on thyroxine replacement 0.1 mg/day . The elevation in alkaline phosphatase, which persisted throughout the illness, was subsequently found to be due to gallstones, which were discovered when the patient suffered an episode of obstructive jaundice three months after ^{131}I therapy. Following surgical treatment, alkaline phosphatase and GGT levels fell to normal.

Discussion

Particularly in elderly patients, severe thyrotoxicosis may occasionally present with few classical manifestations, but rather with non-specific symptoms such as apathy, confusion, malaise and weight loss – the syndrome of 'masked' or 'apathetic' thyrotoxicosis.⁸ While thyroid hormone excess is a recognized cause of hypercalcaemia,^{8,9} the latter is seldom a predominant manifestation of thyrotoxicosis. In this patient, however, both of these unusual clinical features occurred in combination with normalization of circulating thyroid hormone levels leading to diagnostic confusion, and a number of unnecessary investigations.

Serum thyroid hormone levels may be suppressed in euthyroid¹⁻⁴ and hyperthyroid⁵⁻⁷ patients who have a severe non-thyroidal illness. In this case, a number of factors could be implicated in causing suppression of thyroid hormone levels, including malnutrition and weight loss,¹⁰ treatment of hypercalcaemia with glucocorticoids,^{11,12} frusemide,¹³ propranolol therapy¹⁴ and a chest infection.^{1,11,12} In view of the subsequent demonstration of gallstones in this patient, it is possible that the episode of chest pain which was attributed to chest infection during her hospital admission may, in fact, have been due to acute cholecystitis, a condition which has also been associated with the sick euthyroid syndrome.⁵ Whatever the relative contribution of these or other factors, it is evident that when compared with the radionuclide studies, biochemical measurements after admission were an unreliable guide to thyroid status in this patient. Although the TRH test has been considered to be a useful means of excluding thyrotoxicosis in this situation,^{4,15,16} a 'flat' response of TSH to TRH injection is not diagnostic of thyrotoxicosis and may occur in euthyroid individuals with some chronic illness.^{15,16}

From our observations, we would suggest that radio-nuclide studies, although largely superseded by biochemical techniques in routine clinical practice, may

provide a valuable index of thyroid status in sick patients when circulating thyroid hormone levels are difficult to interpret.^{12,14}

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