Unusual presentation of more common disease/injury

An unusual case of hyperthyroidism associated with jaundice and hypercalcaemia

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Summary

A 51-year-old woman with rheumatoid arthritis presented with a 3 month history of painless jaundice and significant weight loss and constipation. Laboratory values were consistent with hyperthyroidism, cholestatic jaundice and parathyroid hormone-independent hypercalcaemia. Three months after beginning of methimazole, euthyroidism was achieved and serum adjusted calcium, total and direct bilirubin levels were normal.

BACKGROUND

Non-specific abnormalities of liver function tests are common in hyperthyroidism and serum bilirubin levels are elevated in about 30% of cases.¹ In contrast, jaundice is rare in such patients and generally occurs together with congestive heart failure secondary to thyroid storm. However, rare cases of overt hyperthyroidism or subclinical hyperthyroidism with severe cholestasis without heart failure have been reported.^{1–4}

Hypercalcaemia occurs in hyperthyroidism alone or due to concurrent hyperparathyroidism. Asymptomatic serum calcium elevation has been documented in up to 20% of cases with hyperthyroidism and is related to increased bone resorption.⁵

Symptomatic hypercalcaemia has been reported as an uncommon occurrence with hyperthyroidism, with calcium levels rarely exceeding 12 mg/dl.^{6,7}

We report the case of a patient with hyperthyroidism who presented with jaundice and hypercalcaemia.

CASE PRESENTATION

A 51-year-old woman presented with a three month history of painless jaundice and weight loss of 8 kg. For the past week, she had been troubled with vomiting, thirst symptoms and constipation. She had rheumatoid arthritis and was treated with hydroxychloroquine for 8 years. She had no history of smoking, abuse of alcohol and blood transfusion. On physical examination, she was markedly icteric with no signs of chronic liver disease or tattoos evident. She was tachycardia and obviously dehydrated. There were no signs of thyroid ophthalmopathy. The thyroid gland was non-palpable and there were no lymphadenopathy or organomegaly on abdominal examination.

INVESTIGATIONS

Pertinent laboratory values included a thyroid stimulating hormone (TSH) of below 0.0038 uIU/ml (normal 0.35 to 4.94) with a free T4 of 2.73 ng/dl (normal 0.7–1.48) and a free T3 of 5.23 pg/ml (normal 1.71–3.71),

consistent with diagnosis of thyrotoxicosis. TSH receptor and thyroid peroxidase antibodies were negative. Results of routine renal and hepatic function tests were 4.5 mg/dl (normal 0.6–1) for creatinine (Cr), 18 mg/dl (normal 0–1) for total bilirubin, 14 mg/dl (normal 0–0.3) for directed bilirubin (DB), 174 U/l (normal 50–136) for alkaline phosphatase, 39 U/l (normal 5–55) for γ -glutamyltransferase, 124 U/l (normal 15–37) for aspartate aminotransferase, 68 U/l (normal 30–65) for alanine aminotransferase and 32 g/l (normal 34–50) for albumin. Peripheral blood was negative for the antibody to hepatitis B surface antigen, immunoglobulin M (IgM) antibody to hepatitis B core antigen, IgM antibody to hepatitis A, hepatitis C virus, HIV and autoantibodies (antinuclear, antimitochondrial, antismooth muscle antibodies). The patient's serum adjusted calcium was 17.8 mg/dl (normal 8.8–10.48) and serum phosphorus of 4.8 mg/dl (2.5–4.9). The parathyroid hormone (PTH) level was 15 pg/ml (normal 15–65) and the 25-OH vitamin D was 11.1 ng/dl (normal >30).

Abdominal ultrasonography and computerised abdomen showed normal liver, biliary tree and gall bladder with no evidence of biliary obstruction. Thyroidal ultrasonography showed normal size and homogenous parenchymal echogenicity of the thyroid gland with diffuse increase vascularity. Further investigations for searching underlying malignancy such as computerised chest and abdomen, bone marrow biopsy, nasopharyngeal biopsy, random skin biopsy and cervical swab were unrevealing.

DIFFERENTIAL DIAGNOSIS

1. Hyperthyroidism with jaundice
 - Intrinsic biliary tract obstruction
 - Drug/toxin induced cholestasis
 - Primary biliary cirrhosis/primary sclerosing cholangitis
2. Hyperthyroidism with hypercalcaemia
 - Hyperparathyroidism
 - Humoral hypercalcaemia of malignancy

TREATMENT

We considered that jaundice and hypercalcaemia had developed secondary to hyperthyroidism. Methimazole 10 mg/day and cholestyramine at doses ranging from 4–5 g/day were initiated. She was treated with saline hydration, furosemide and a single dose of pamidronate (30 mg).

OUTCOME AND FOLLOW-UP

Ten days later, the serum adjusted calcium level normalised to 9.5 mg/dl. Seventeen days later, the serum total and DB levels had fallen to 8 mg/dl and 5.9 mg/dl, respectively. Three months after beginning of antithyroid treatment, euthyroidism was achieved and serum adjusted calcium, total and DB levels were normal at 10 mg/dl, 1.2 mg/dl and 0.5 mg/dl, respectively.

DISCUSSION

Thyroid hormone concentrations are important for normal hepatic function and metabolism of bilirubin. This partly explains the complexity of thyrotoxicosis that be associated with various abnormalities in liver function and can be the cause of profound cholestasis. Hyperthyroidism induces an increased metabolic rate, which is associated with increased hepatic oxygen consumption and oxidative damage of tissue without increasing the hepatic blood flow, thus lowering the oxygen tension in the centrilobular zones and interfering with bile transport, probably resulting in cholestasis and increasing the rate of bile flow to the point of saturation.^{8–10} It is suspected that excess thyroxine can produce direct toxic effect on hepatocytes; however, there are no available data supporting this.⁹ We choose methimazole for this case because methimazole-induced jaundice appears to be a idiosyncratic reaction and occurs in a handful of cases.¹¹ In the other hand, propylthiouracil mainly causes hepatocellular damage and this side effect is dose-related.¹² However, it has been reported that methimazole and cabimazole were successfully used in restoring euthyroidism as well as ameliorating the hyperthyroidism-related jaundice.^{1–3} Lack of knowledge of the association between thyroid and liver abnormalities can lead to misdiagnosis, mistakes in management of patients and consequent under-reporting of those patients affected.

The most common cause of hypercalcaemia in thyrotoxicosis is concurrent with primary hyperparathyroidism. In 15–20% of cases however, alterations of calcium metabolism are related to the thyrotoxicosis alone.¹³ Our case demonstrates hypercalcaemia secondary to thyrotoxicosis alone, as supported by low PTH level and resolution of hypercalcaemia with treatment of the thyroid disease. The proposed mechanism of hypercalcaemia is enhanced bone resorption, unrelated to PTH levels. Triiodothyronine is known to increase the sensitivity of the bone to interleukin

(IL)-6. High circulating levels of IL-6 seen in hyperthyroidism stimulate bone osteoclastic activity and alter the osteoblast-osteoclast coupling.¹⁴ The PTH levels in hypercalcaemia of thyrotoxicosis are either suppressed or low normal. The increased metabolic clearance rates in thyrotoxicosis could also lower the PTH levels. The definitive treatment for hypercalcaemia in thyrotoxicosis is correction of underlying thyroid disease.¹³

Learning points

- Jaundice and symptomatic hypercalcaemia are unusual presentation of hyperthyroidism that resolves once the hyperthyroidism has been treated.
- Methimazole was used in ameliorating the hyperthyroidism-related jaundice.
- Routine plasma calcium should be performed in cases of hyperthyroidism
- Exclusion of malignancy is always important in the differential diagnosis of hypercalcaemia.

Competing interests None.

Patient consent Obtained.

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