Deep cholestatic jaundice and pulmonary hypertension in a woman with Graves' hyperthyroidism

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INTRODUCTION

Hyperthyroidism is associated with relative hepatic hypoxia, which can result in a spectrum of hepatic dysfunction. Abnormalities have been reported in the presence or absence of complicating congestive heart failure. Sherlock (1985) asserts that the major cause of cholestatic jaundice in untreated hyperthyroidism is congestive heart failure. The association between pulmonary hypertension and hyperthyroidism has been described since the early 1980s (Shimazaki et al, 1980). The prevalence of hypothyroidism in pulmonary hypertension is 22.5% (Nakchbandi et al, 1999). However, only a few cases have been reported to have pulmonary hypertension with hyperthyroidism. This article reports a rare case of pulmonary hypertension and cholestatic jaundice in a woman with hyperthyroid Graves' disease. The patient completely recovered after the hyperthyroid state and right-sided heart failure were treated.

CASE REPORT

A 28-year-old woman, gravida 0, parity 0, had hyperthyroidism 6 years ago and had been treated with antithyroid drugs for 3 years. She discontinued the drugs when she returned to the euthyroid state. Her hyperthyroid symptoms recurred a few months after she withdrew the medication and she received Chinese herbal medicine as the only treatment. Progressive generalized oedema, severe dyspnoea, orthopnoea and deep-coloured urine were noted about 4 months before admission. Secondary amenorrhoea for 3 months and gynaecological ultrasound revealed ascites only. Family history revealed that her grandmother, mother and younger sister had hyperthyroidism as well and her sister has also thalassaemia.

Physical examination on admission revealed a critically-ill woman with severe orthopnoea, generalized oedema, hand tremor and icterus. Her weight was 61.5 kg, height 160 cm, blood pressure was 120/90 mmHg, body temperature was 37.6°C, and pulse rate was 145 beats per minute (sinus tachycardia). She was alert. Haemotological investigations revealed microcytic anaemia and her haemoglobin (Hb) was 4.8 mmol/litre. The serum total bilirubin was 478.8 mmol/litre with direct bilirubin 224.0 mmol/litre, aspartate aminotransferase 32 u/litre, alanine aminotransferase 70 u/litre, γ-glutamyl transferase 5 u/litre and alkaline phosphatase 83 u/litre. The prothrombin time was normal and serum albumin level was 32 g/litre. Hb electrophoresis indicated α thalassaemia. Serological markers for hepatitis A, B and C were absent. High titre of antinuclear antibody (1:160, homogenous) and CA-125 (1075.4 U/ml) were noted, but the D-coombs' test was negative, as were tests for C3, C4, antismooth muscle antibody, antimitochondrial antibody, antidouble strand antibody and lupus anticoagulant. Cytological examination of ascites and pleural effusion indicated transudate with lymphocyte predominance.

The total thyroxine level was high at 271.3 nmol/litre and the thyroid-stimulating hormone level measured by sensitive radioimmunoassay was depressed at less than 0.03 mU/litre. Although serum microsomal antibody titres were negative, thyroid binding inhibitory immunoglobulin was positive (64.8%).

Chest X-ray revealed massive pleural effusion on the right side and moderate effusion on the left side (*Figure 1*). Abdominal ultrasound showed normal liver size, non-cirrhotic liver with moderate ascites, and bilateral pleural effusion. Gynaecological ultrasound revealed moderate ascites, but could detect no tumour. A two-dimensional echocardiogram reported severe tricuspid regurgitation, moderate pulmonary hypertension and cor pulmonale. A diffusion lung capacity test was positive. The patient was thought to have primary hyperthyroidism with pulmonary hypertension and cholestatic jaundice, and was treated with furosemide 40 mg/day, polythiouracil 300 mg/day and propanolol 40 mg/day. Three weeks later, the serum total bilirubin and CA-125 had decreased to 44.5 mmol/litre and 29.6 U/ml respectively. She loss 10 kg in weight and the generalized oedema subsided. The patient's condition improved and laboratory tests yielded normal results. *Figure 2* shows the serial serum bilirubin results.

DISCUSSION

Although hyperthyroidism associated with cholestatic jaundice or pulmonary hypertension has been reported (Greenberger et al, 1964; Thompson et al, 1978; Martos Velasco, 1992; Alcazar et al, 1995; Thurnheer et al, 1997), to the authors' knowledge this is the only second article describing a hyperthyroid patient with concurrent cholestatic jaundice and pulmonary hypertension (Mozo Herrera et al, 2001). This patient is different to the previously reported case in three respects. First, she is a young female with autoimmune hyperthyroidism, in contrast to a 66-year-old female with toxic nodular goitre. The cholestatic jaundice in this patient was far more severe (478.8 mmol/litre *vs* 119.7 mmol/litre). Finally, the reason that this patient presented fulminantly during the second episode of hyperthyroidism rather than during her first episode of hyperthyroidism remains unclear.

Many researchers have reported the relationship between the hyperthyroid state and pulmonary hypertension. The condition is reversible but often neglected clinically. Nakchbandi et al (1999) suggested that high cardiac output, endothelial damage, or increased metabolism of intrinsic pulmonary

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vasodilating substances probably cause pulmonary hypertension in patients with hyperthyroidism. However, Arroliga et al (2000) reported that electrical stimulation of the sympathetic nerves causes pulmonary vasoconstriction, reduced pulmonary artery compliance, and increased pulmonary vascular resistance. The elevated antinuclear antibody titre suggested that autoimmune processes might also have contributed to pulmonary hypertension in this patient. Whether pleural effusion contributes to the development of pulmonary hypertension needs further investigation.

Non-specific hepatic dysfunction has been found in up to 76% of hyperthyroid patients. Cholestasis in hyperthyroidism has three potential causes: relative hepatic hypoxia, congestive heart failure and direct toxic effect of thyroxine on the liver. Mild cholestasis generally occurs, along with congestive heart failure, as a result of severe thyrotoxicosis. This patient's left ventricular function was normal. Severe jaundice developed without evidence of viral hepatitis, primary biliary cirrhosis or drug hepatitis (normal alkaline phosphatase and gamma glutamyl transferase). The serum total bilirubin rapidly fell to normal within 3 weeks, in contrast to the fact that most patients with hepatic dysfunction caused by hyperthyroidism recovered gradually within 3 months. Nevertheless, her condition improved in parallel with the improvement of her right heart function. Treatment for hyperthyroidism and right-sided heart failure rapidly resolved both conditions. Congestive heart failure might be the main cause of her cholestasis, rather than a hyperthyroid state.

Elevated CA-125 is a non-specific marker related to ascites. It rapidly decreased to normal when ascites subsided. The cause of lymphocyte predominant cytology obtained from ascites and pleura remains unclear. Autoimmune thyroid disease or obstruction of the lymph might be associated with this phenomenon, but no previous literature has reported this. The possibility of tuberculosis in this patient has not been totally excluded.

CONCLUSIONS

This article described a patient with recurrent hyperthyroidism, followed by pulmonary hypertension and right-sided heart failure, which led to cholestatic jaundice. All symptoms rapidly resolved after diuretic and antithyroid drugs were prescribed. This case emphasizes that intrahepatic cholestasis associated with thyrotoxicosis may be severe, especially in the presence of congestive heart failure. Hyperthyroidism should be considered in the differential diagnosis of cholestasis and/or pulmonary hypertension. HM

Figure 1. a. Chest X-ray demonstrates bilateral moderate to severe pleural effusion (right side predominant). b. The pleural effusion completely resolved after treating hyperthyroid state.

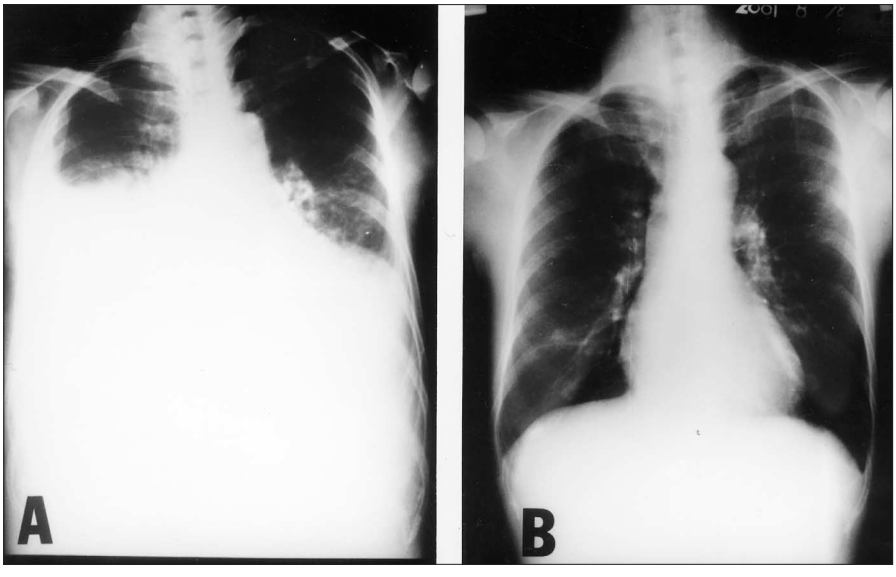
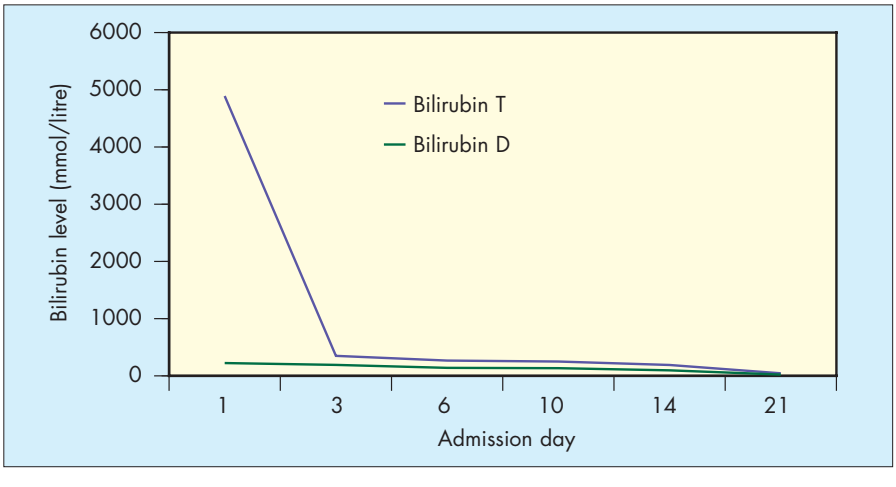


Figure 2. Liver profile of the patient. The deep jaundice rapidly fell to the normal range within 3 weeks.



Alcazar R, Rey M, de Sequera P, Alegre R, Rovira A, Caramelo C (1995) The reversibility of pulmonary hypertension associated with autoimmune hyperthyroidism. *Rev Esp Cardiol* **48:** 142–4

Arroliga AC, Dweik RA, Ratanan AL (2000) Primary pulmonary hypertension and thyroid disease. *Chest* **118:** 1224–5

Greenberger NJ, Milligan FD, DeGroot LJ, (1964) Jaundice and thyrotoxicosis in the absence of congetive heart failure. A study of four cases. *Am J Med* **36:** 840–6

Martos Velasco J (1992) Primary pulmonary hypertension associated with hyperthyroidism. *Aten Primaria* **9:** 163–4

Mozo Herrera G, Fernandez Gonzalez MJ, Salgado Blanco J et al (2001) Hyperthyroidism, Jaundice, and pulmonary hypertension. *An Med Interna* **18:** 262–4

Nakchbandi IA, Wirth JA, Inzucchi SE (1999) Pulmonary hypertension caused by Graves' thyrotoxicosis: normal pulmonary hemodynamics restored by 131I treatment. *Chest* **116:** 1483–5

Sherlock S (1985) *Disease of Liver and the Biliary System.* 7th edn. Blackwell Scientific Publications, Boston: 399–400

Shimazaki M, Mitsuhashi T, Hasegawa K (1980) Idiopathic pulmonary hypertension associated with hyperthyroidism: an autopsy case. *Nippon Rinsho* **38:** 1783–6

Thompson P Jr, Strum D, Boehm T et al (1978) Abnormalities of liver function tests in thyrotoxicosis. *Milit Med* **143:** 548–51

Thurnheer R, Jenni R, Russi EW et al (1997) Hyperthyroidism and pulmonary hypertension. *J Intern Med* **242:** 185–8