

Liver Cholestasis in Thyrotoxicosis: a Case Report

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Thyrotoxicosis is often associated with liver and malfunction, often for long durations; sometimes the liver function is substantially impaired for a longer period of time. The exact nature however of the relation between hepatic dysfunction and thyrotoxicosis remains obscure. Presented here is a case report of liver cholestasis as a complication of thyrotoxicosis.

Materials and Method: A previously healthy 41-year-old man with thyrotoxicosis complicated with liver cholestasis is discussed.

Results: The patient reported had a typical thyrotoxicosis but following radioiodine treatment concomitantly developed jaundice and severe pruritus that required several weeks of treatment in hospital and took several months to disappear. In this report the therapeutical considerations as well as the pathogenetic possibilities are reviewed.

Conclusion: The association observed is not common but may be severe and should be considered in any case of thyrotoxicosis where a cholestatic condition develops.

Key Words: Case report, cholestasis, Graves' hyperthyroidism, liver disease; radioiodine; thyrotoxicosis

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Introduction

Hepatic dysfunction in patients with thyro-

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toxicosis was described as early as 1874.¹ Abnormal liver-function tests occur in a significant minority of thyrotoxic patients.² In severe thyrotoxicosis, thyroid storm, multiple organ dysfunction with liver dysfunction is described.^{3,4} The condition may develop into severe hepatic dysfunction and even death may occur.^{1,5} However, the exact nature of the relation between thyrotoxicosis and hepatic dysfunction remains elusive. Cholestasis has been reported to be a dominant feature.^{6,7} In rats, excess triiodothyronine (T3) causes liver dysfunction by induction of apoptosis through mitochondria-dependent pathways.⁸

We report a patient with severe cholestasis and pruritus in association with thyrotoxicosis and other possible alternative diagnoses are reviewed.

Case report

A previously healthy 41-year old man, ex-smoker, without any medication usage presented with a 14-kg weight loss, sweating, fine hand tremor and generalised pruritus. Clinical examination revealed a diffuse goitre, finger tremor and warm skin. Serum concentration of TSH was <0.04 mU L⁻¹ (0.10-6.0) and of free thyroxine (FT4) was 64 pmol L⁻¹.¹²⁻²⁴ Thyrotropin receptor antibodies were demonstrated and thyrotoxicosis of Graves' type was diagnosed. The patient was

treated with radioactive iodine, 150 Gray. A week before radioiodine was administered the serum concentration of bilirubin was 64 $\mu\text{mol L}^{-1}$ (<20), of aspartate aminotransferase (AST) was 1.24 ukat L^{-1} (<0.70), of alanine aminotransferase (ALT) was 2.73 ukat L^{-1} (<0.70) and of alkaline phosphatase (ALP) was 7.4 ukat L^{-1} (<4.6). Despite this the patient had not yet developed any overt signs of jaundice or pruritus. Three weeks later the patient was admitted to hospital due to troublesome pruritus. He had signs of persisting thyrotoxicosis with a serum thyroxine (T4) level of 220 nmol L^{-1} (50-150), and now clinically overt icterus had developed. The serum concentration of total bilirubin was 101 $\mu\text{mol L}^{-1}$ (<20), of direct bilirubin was 82 $\mu\text{mol L}^{-1}$, of aspartate aminotransferase (AST) was 1.68 ukat L^{-1} (<0.70), of alanine aminotransferase (ALT) was 3.29 ukat L^{-1} (<0.70) and of alkaline phosphatase (ALP) was 6.9 ukat L^{-1} (<4.6), even if the prothrombin time of normal albumin was below cut-off; 30 g L^{-1} (40-51). No signs of cardiac insufficiency could be identified. Despite clinically manifest thyrotoxicosis the pulse rate was 70 beats/minute and the blood pressure 150/70 mm Hg. He had no peripheral edema and a pulmonary X-ray was normal.

A thorough investigation was carried out in order to exclude any kind of primary liver disease. Serum antibodies against hepatitis A, B and C and against smooth muscle and mitochondria were absent. Antibodies against adeno virus, CMV, herpes simplex type 1 and varicella-zoster were present in serum as IgG in low titres but not IgM. Serum levels of immunoglobulins IgG, IgA and IgM were all within normal range. Serum levels of iron were normal; 16 $\mu\text{mol L}^{-1}$ (10-30) and total iron binding capacity slightly decreased; 43 $\mu\text{mol L}^{-1}$ (45-72). Alpha-1- antitrypsin concentration in serum was within normal range. Plasma-copper concentration was 31 $\mu\text{mol L}^{-1}$ (11-25) and total urine-copper 2.9 $\mu\text{mol (24h)}^{-1}$ (<2), but ceruloplasmin was not decreased and no Kayser-Fleischer ring could

be observed. The hemoglobin level was normal and blood reticulocytes as well as haptoglobin were within the normal range. Further investigation included abdominal ultrasonography and endoscopic retrograde cholangiopancreatography, both normal. Two histological examinations of the liver revealed isolated cholestasis.

During the weeks following admission to hospital, the bilirubin levels increased further and the pruritus became concomitantly more severe (Fig.1) and was not relieved by medication. The patient also had clinical and laboratory signs of persisting thyrotoxicosis; serum T4 concentration was 220 pmol L^{-1} (50-150) and TSH $<0.1 \text{ mU L}^{-1}$ (0.10-6.0). Since the effect of radioactive iodine is delayed, methimazole (Thacapzol) 15 mg b.i.d. was added. Plasmapheresis was carried out four times with a temporary favourable effect for almost three weeks after which the patient's pruritus started to reappear. Finally, treatment with prednisone helped reduce the pruritus.

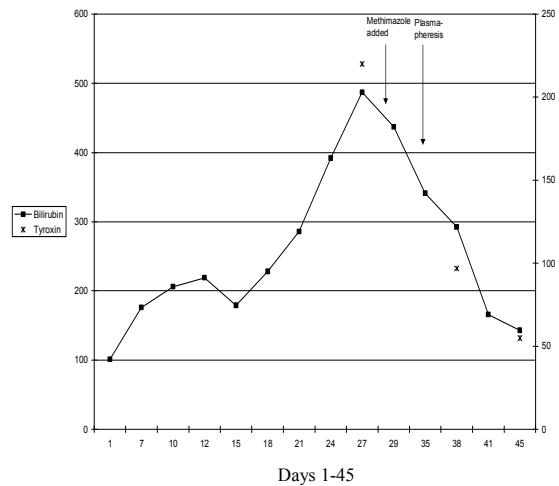


Fig.1. Disease course from day of admission

* Serum bilirubin concentration ($<20 \mu\text{mol L}^{-1}$) is stated on the left y axis and serum thyroxine (T4) concentration (50-150 nmol L^{-1}) on the right. Time for treatment (methimazole and plasmapheresis) is indicated with arrows

Two months after the radioiodine treatment and the following methimazole-medication, thyroid parameters were within normal range.

The prednisone medication was discontinued and the pruritus could be controlled with antihistamines. It was not until ten months after the onset of jaundice that all liver parameters returned to normal. The patient's liver function has remained stable, but a year after the radioiodine treatment hypothyroidism developed and thyroid hormone replacement therapy was introduced.

Discussion

The present patient had concomitant thyrotoxicosis and cholestasis. He was investigated according to ordinary considerations concerning the cause of liver disease including a liver biopsy. In this, isolated cholestasis could be seen, which was in accordance with the liver enzymes that showed predominant signs of cholestasis.

The possibility of primary liver disease could be ruled out. No evidence for immunological conditions (autoimmune hepatitis, primary sclerosing cholangitis or primary biliary cirrosis) was found; neither was metabolic liver disease due to α -1 antitrypsin deficiency, hemochromatosis or Wilson's disease identified. Although the copper levels in plasma and urine were increased, no other signs of Wilson's disease were present and the course of the disease made it less likely. Furthermore, increased copper concentration is often seen secondary to cholestasis. Hepatitis serology was negative and serology for several other virus infections that might lead to liver dysfunction did not indicate presence of active virus infection. The patient's alcohol consumption was sparse limited to less than one drink a month.

Thus, since no evidence of primary liver disease was present a secondary cause had to be considered. Congestive heart failure has been described as a cause of impaired liver function.⁹ However, no symptoms or signs of cardiac failure could be identified in our patient. Abdominal ultrasonography was normal and examination of the liver histology

only revealed cholestasis but no signs of liver dysfunction due to heart failure.

In view of these considerations and especially in view of the course of events the most probable explanation for the liver disease was the preceding thyrotoxicosis. The relationship between thyrotoxicosis and liver disease especially in earlier reports has been recognised; 15% in 570 patients with thyrotoxicosis had at least one abnormality in liver function tests and in another study the overall incidence of abnormality was 76% in 85 patients with improved liver function as the patients became euthyroid.^{10,11,12} Different theories regarding the pathogenetic mechanisms have been postulated. One theory is that the hepatic oxygen consumption is increased more than the hepatic blood flow resulting in reduced oxygen tension in the centrilobular zones.¹³ A toxic effect of thyroxine has also been hypothesised^{5,6} and a direct impact on liver function of elevated thyroid hormones has been shown in experiments on rats.¹⁴ One possible explanation to this effect could be the fact that excess T3 causes liver dysfunction in rats by induction of apoptosis through mitochondria-dependent pathways.⁸

However, there is still no firm evidence that thyroid hormone is directly toxic to the liver.² In addition it is important to consider that liver function abnormalities in thyrotoxic patients may be induced by anti-thyroid drugs, which was illustrated in a recent case report; a 36-year-old Chinese man, with symptoms of thyrotoxicosis neglected for one year, was treated with carbimazole 10 mg three times daily. Due to an urticarial rash after two weeks of treatment, medication was switched to propylthiouracil 100 mg three times daily. Two weeks later he developed jaundice and later died from liver failure and pneumonitis. Numerous glycogen inclusion bodies could be seen in the liver biopsy as well as prominent intracanalicular cholestasis,¹⁵ findings compatible with a drug induced injury. Data reviewed on hepatotoxicity indicates that low-dose methimazole is safer than propylthiouracil.¹⁶ Propylthiouracil

hepatotoxicity often occurs in younger patients, while methimazole toxicity is more common in patients over 40 years old. The patient reported in the present study was 41 years old, and the drug chosen can of course be discussed. On the other hand, in view of the course of disease, the most probable cause for the liver injury was the thyrotoxicosis and not the treatment. It is apparent from the laboratory analyses that the liver was already affected before methimazole was introduced.

Recently a 39-year old man with severe cholestatic jaundice in thyrotoxicosis was reported.¹⁷ The jaundice appeared following treatment with radioiodine. To our knowledge, jaundice as a complication of radioiodine therapy has not been described elsewhere. However, glomerulonephritis due to circulating thyroglobulin-anti-thyroglobulin immune complexes following radioactive iodine treatment has previously been described.¹⁸ Whether a similar mechanism was able to cause liver damage is open to speculation. Thus, other disease modifying factors—maybe of immunological origin—have to be contemplated.¹⁸ The complicated course of the disease in our patient is comparable to that of a patient described by Joseph Yao and co-workers.⁶ Their patient also had pruritus and icterus and marked cholestasis but with an acceptable response to thyroid-ablative treatment with radioactive iodine and recovery

of jaundice after approximately one month. Three months later he could return to work full-time and had normal thyroid parameters. This disease course indicates that, at least in this patient, it was the thyrotoxicosis rather than the radioiodine treatment that was responsible for the jaundice. In propylthiouracil-associated hepatotoxicity the prognosis was superior in those who had been treated with radioiodine as compared to those without the treatment, something that contradicts the hypothesis that radioiodine should have a pathogenetic role, at least in that kind of hepatotoxicity.¹⁹ Our patient had normalised thyroid function after two months but persisting liver disease where the transaminases were normal first after ten months. Consequently, it should be noted that the convalescence of this kind of disease may be rather long.

Liver dysfunction in thyrotoxicosis is important to recognise, since the liver function may be severely impaired and the condition in rare cases may even lead to death.¹ A prompt diagnosis and an appropriate treatment is therefore important in such cases. In the patient reported, combined therapy against the thyrotoxicosis had to be given. To facilitate a quick prompt diagnosis, an awareness of the condition is essential, even though patients with more substantial liver dysfunction are rare, the association should be considered in any case of thyrotoxicosis where a cholestatic condition develops.

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