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Cholestatic Jaundice as a Rare Manifestation of Hyperthyroidism: A Case Report and Review

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Abstract **Case Report**

Thyroid hormones, including thyroxine (T4) and triiodothyronine (T3), play a crucial role in regulating the basal metabolic rate of all cells, including hepatocytes, thereby influencing liver function. While hepatic dysfunction is frequently observed in hyperthyroidism, it is often mild and asymptomatic. However, cholestatic jaundice as a primary manifestation of hyperthyroidism is exceedingly rare. We report the case of a 33-year-old patient presenting with jaundice and pruritus. Laboratory tests revealed elevated alanine aminotransferase (1.4× upper limit of normal [ULN]), aspartate aminotransferase (1.6× ULN), alkaline phosphatase (3× ULN), gamma-glutamyl transferase (1.4× ULN), and bilirubin (183.4 µmol/L). Abdominal ultrasound was unremarkable, and extensive investigations ruled out toxic, drug-induced, infectious, autoimmune, and obstructive biliary causes. Thyroid function tests demonstrated elevated free T4 (23.6 pmol/L; normal: 9.01–19.05 pmol/L) with suppressed TSH (<0.005 µIU/mL; normal: 0.35–4.94 µIU/mL), and positive TSH receptor antibodies (8.3 IU/L; normal: <1.5 IU/L). Thyroid ultrasound revealed a diffuse, hypervascular goiter, confirming the diagnosis of Graves' disease with hepatic involvement, in the absence of cardiac dysfunction. The patient's condition improved significantly with carbimazole treatment. This case highlights the importance of considering hyperthyroidism in the differential diagnosis of unexplained cholestatic jaundice. Early recognition and appropriate management can prevent unnecessary interventions and ensure favorable outcomes.

Keywords: Hyperthyroidism, Cholestatic Jaundice, Hyperbilirubinemia.

INTRODUCTION

Thyroxine and tri-iodothyronine are essential for normal organ growth, and development and function of human body. These hormones regulate the basal metabolic rate of all the cells, including hepatocytes, and thereby, modulate hepatic functions. Thus, thyroid dysfunction may perturb liver function [1]. Although rare, the presentation of severe cholestatic jaundice in thyrotoxicosis has been described in the literature. The proposed mechanisms underlying liver dysfunction in hyperthyroidism include direct liver toxicity due to prolonged excessive thyroid hormone exposure, hepatocyte anoxia and free radical damage resulting from the hypermetabolic state, hepatocyte degeneration due to accelerated liver glycogen and protein breakdown, autoimmune-related liver disease, congestive hepatopathy secondary to concomitant thyrotoxic heart failure, pre-existing liver conditions, and liver toxicity and injury associated with antithyroid medications [2-4]. We present the clinical history and laboratory findings of a patient who presented with cholestatic jaundice, with eventual improvement following the administration of antithyroid drugs. It is crucial to consider thyrotoxicosis in patients with jaundice of unknown origin and to evaluate the use of antithyroid drugs for treating hyperbilirubinemia associated with thyrotoxicosis.

CASE PRESENTATION

A 33-year-old male presented with a history of jaundice and generalized pruritus of one month duration without any history of viral prodrome, drug intake or fever. The patient was non-alcoholic. The patient is a non-diabetic and had no comorbid illness. There was no family history of jaundice or liver disease. He also reported weight loss of 6 kg in tow months.

Clinical examination revealed marked cutaneous-mucosal jaundice with scratching lesions. The heart rate was 105 beats per minute. The remainder of the clinical examination was normal, with no goiter, exophthalmos, hepatosplenomegaly, or signs of heart failure. Liver function tests showed ALT 58 IU/L, AST

80IU/L, ALP 387 IU/L, GGT 99.4 IU/L, and Hyperbilirubinemia was observed with a total bilirubin level of 183.4 µmol/L with direct fraction of (158 µmol/L). The albumin level was 40 g/L. Coagulation profile, renal function tests and lipid profile were within normal limits.

Hepatic serologies (HbsAg, HCV) were negative. Autoimmune markers, anti-mitochondrial antibodies, anti-smooth muscle antibodies, anti soluble liver antigens, anti liver cytosol antibodies, anti–liver-kidney microsomal antibodies, and anti-nuclear antibodies were negative. Abdominal ultrasound findings were unremarkable. Magnetic resonance cholangiopancreatography (MRCP) revealed no dilation of the intra- or extra-hepatic bile ducts, with both the pancreas and liver appearing normal. A liver biopsy showed findings consistent with cholestatic hepatitis, with no evidence of autoimmune hepatitis. Keeping in view sinus tachycardia patient was further evaluated and found to have electrocardiogram suggestive of sinus tachycardia with no ectopics. Echocardiography was normal. Thyroid function tests indicated elevated free T4 of 23.6 ng/dL (normal range: 9.01-19.05 pmol/L) and an undetectable TSH level of less than 0.005 µIU/mL(normal range: 0.35-4.94 µIU/mL). TSH receptor antibodies were positive of 8.3 IU/L (normal value: <1.5 IU/L). Thyroid ultrasound showed a diffuse, homogeneous, hypervascular goiter. He was started on anti-thyroid treatment Tablet carbimazole 10 mg daily once daily and Tablet propranolol 40 mg daily once daily. Clinically, the patient showed regression of jaundice and pruritus, along with a 5 kg weight gain. Patients heart rate settled to 74 beats per minute. Biological tests conducted three months after the initiation of treatment demonstrated normalization of free T4, TSH, transaminases, bilirubin, GGT, and a reduction in alkaline phosphatase levels to 1.2xULN (Table 1).

Table 1: Biochemical investigation of patient before treatment and at 3 months follow up

Parameter	Before treatment	Follow up after 3 months
Total bilirubin (µmol/L)	183.4	9
Direct bilirubin (µmol/L)	158	5
AST (IU/L)	80	45
ALT (UI/L)	58	39
ALP (UI/L)	387	154.8
GGT (UI/L)	99.4	62
TSH (µIU/mL)	0.005	0.37
fT4 (ng/dL)	23.6	17

DISCUSSION

Thyroid hormones are essential in regulating thermogenesis and human metabolism, exerting their effects through the modulation of various cell types, including hepatocytes, which in turn influence hepatic function. Moreover, liver cells play a critical role in the regulation of thyroid hormones, encompassing processes such as hormone activation and inactivation, transport, and metabolism. Up to 85% of thyroxine (T4) is converted to triiodothyronine (T3) in peripheral tissues, primarily by liver cells. Additionally, the liver synthesizes plasma proteins that bind up to 99% of the thyroid hormones circulating in the plasma [1-5]. Thyrotoxicosis is a condition characterized by an excess of circulating thyroid hormones, irrespective of the underlying etiology [5].The global prevalence of thyrotoxicosis is estimated to range from 0.2% to 1.3% in regions with adequate iodine levels, with a higher incidence observed in females [6]. Graves' disease is the leading cause of hyperthyroidism, primarily affecting young to middle-aged individuals, with a higher prevalence in women [7].

Hepatic dysfunction is a common finding in patients with thyrotoxicosis, with abnormal liver enzyme levels reported in 15–75% of cases [8, 9]. The first description of liver injury secondary to isolated hyperthyroidism, in the absence of cardiac involvement, dates back to 1874 [10]. Since then, multiple cases have been documented in the literature [11-13].

The exact mechanism underlying liver toxicity in the hyperthyroid state remains poorly understood. Hyperthyroidism increases the metabolic rate, which can lead to a relative reduction in blood flow to certain regions of the liver, resulting in hypoxic injury. Additionally, thyroid hormones may exert a direct toxic effect on hepatic tissue. Studies in rats have shown that hyperthyroidism reduces the activity of bilirubin UDP-glucuronosyltransferase, decreases the ratio of bilirubin di- to monoconjugates in both bile and plasma, and lowers the ratio of conjugated to total bile pigment concentration in the liver and plasma [2-15]. Furthermore, excessive levels of triiodothyronine can induce hepatocyte apoptosis through a mitochondrial-dependent pathway [2-15].

The Hepatic impairment is most often asymptomatic, but it can sometimes be more severe, leading to jaundice. In some cases, hepatic involvement may be the circumstances under which hyperthyroidism is first discovered, as in our observation.Frank jaundice is rare, occurring in 5% of patients of hyperthyroidism, more common in thyroid storm and implicates a poor prognosis [16]. Liver involvement in hyperthyroidism is

most commonly restricted to abnormalities in liver function tests, which were observed in 75.8% of cases [17]. A systematic review and meta-analysis have shown the prevalence of abnormal liver tests in patients with hyperthyroidism: 23% for AST, 33% for ALT, 44% for ALP, and 12% for bilirubin [18]. However, this data may overestimate the prevalence of cholestatic liver injury, as elevated alkaline phosphatase is not solely specific to hepatic sources. Although increased alkaline phosphatase levels have been observed in up to 67% of thyrotoxic patients, these elevations may be due to hormone-induced cholestasis as well as enhanced osteoblast activity [5-8]. However, a few case reports showed that thyroid storm can cause severe fulminant hepatitis or acute liver failure, with AST and ALT levels rising to several hundred to over 1000 IU/L [19, 20].

The overall incidence of liver abnormalities within 6 months following thyrotoxicosis was 39% [21]. An initial serum TSH concentration <0.02 mUI/L, male sex, and African-American race were significant predictive factors for the occurrence of liver disturbances within 6 months following the diagnosis of recent-onset untreated thyrotoxicosis [21]. The severity of hyperthyroidism is not correlated with the degree of liver test abnormalities [22].

Our patient presents with Graves' disease complicated by hepatic involvement without cardiac dysfunction. The liver injury was attributed to thyrotoxicosis, as toxic or drug-induced causes, biliary obstruction, viral hepatitis B or C, autoimmune hepatitis, and primary biliary cholangitis were excluded. There were no signs suggestive of an acute thyrotoxic crisis. The favorable outcome following treatment with synthetic antithyroid drugs further supports the thyrotoxic origin of this hepatic involvement.

Liver histology predominantly reveals non-specific changes on light microscopy, including mild lobular inflammation, nuclear changes, and Kupffer cell hyperplasia. Mainly two patterns of hepatic injuries are known with thyroxicosis: hepatitic type and cholestatic type [1-12]. In hepatitis pattern of injury relative hypoxia in the perivenular regions, due to an increase in oxygen demand without an appropriate increase in blood flow, seems to be the most probable mechanism which can lead to centrizonal necrosis and perivenular fibrosis in most severe cases which is evident by increase in transaminase levels [1]. In cholestatic type of injury, the most probable mechanism includes the hyper metabolic state in hyperthyroidism which increases the enzyme induction and, the role of venous congestion due to heart failure are stipulated [23]. Another proposed hypothesis is that excessive thyroid hormones may exert a direct toxic effect on hepatocytes. In our case, the patient exhibited a cholestatic pattern, which was further corroborated by the liver biopsy.

Among the factors contributing to liver dysfunction are direct hepatocyte injury, co-morbid heart failure, associated autoimmune diseases, underlying liver disease, and antithyroid drugs. Cholestasis often occurs as a result of thyrotoxicosis, although the underlying process remains unclear [4]. A frequent cause of jaundice in thyrotoxicosis is liver injury induced by various medications, including thionamides, which are initiated upon admission [24]. The incidence of antithyroid-associated hepatic dysfunction is estimated to range from 0.1% to 0.2% [25]. Currently, the risk factors for drug-induced liver injury associated with ATDs remain unclear. However, some studies suggest that advanced age and higher drug doses may increase the risk of liver injury in patients treated with ATDs [26]. Previous studies have shown that methimazole (MMI) is commonly associated with cholestasis, while propylthiouracil (PTU) predominantly causes hepatocellular damage [25]. The MMI group exhibited a higher incidence of the cholestatic type (35.3%) compared to the PTU group (17.9%) in patients with severe hepatotoxicity induced by ATDs. Given that autoimmune mechanisms contribute to liver damage in 10% of patients with Graves' disease, individuals with autoimmune thyroid disorders should undergo screening for other potential autoimmune etiologies as part of their cholestasis evaluation [27]. Therefore, clinicians are frequently confronted with the risk of worsening liver injury in patients with hyperthyroidism and severe jaundice. We did not observe any side effect of the treatment and the patient tolerated the medication well. There was a significant improvement in his symptoms, and liver enzyme levels gradually returned to normal, except for the alkaline phosphatase level, as shown in Table 1. However, it is crucial to rule out other liver diseases in individuals with hyperthyroidism and cholestasis, particularly in regions where outbreaks of hepatitis B or C are prevalent [28]. According to a study by Kang *et al*., a chronic carrier of the hepatitis B virus developed acute liver failure induced by MMI [29].

CONCLUSION

Hyperthyroidism is a well-known but often overlooked cause of hepatic dysfunction. While mild liver enzyme abnormalities are frequently observed, severe cholestatic jaundice as a primary manifestation of thyrotoxicosis remains rare. This case underscores the importance of considering hyperthyroidism in the differential diagnosis of unexplained jaundice, particularly when conventional hepatic and biliary causes have been excluded. Early recognition and appropriate management with antithyroid therapy can lead to significant clinical improvement and prevent unnecessary invasive investigations. A multidisciplinary approach involving endocrinologists and hepatologists is crucial for optimizing patient outcomes.

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