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An unusual case of severe hyperbilirubinemia and thyrotoxicosis

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Objective. We report a case of a 23-year-old pregnant female with five months of amenorrhea. She was referred to us with rapidly developing jaundice, anemia, and dyspnea with hyperthyroidism.

Methods. After initial treatment of all the possible causes of progressive jaundice led to no improvement. The treatment was then heavily directed towards managing thyroid storm.

Results. Hepatic dysfunction improved with iodine and thionamides. Patient recovered well. This points towards the uncommon association of severe hyperbilirubinemia with thyroid storm a potentially fatal endocrine disorder and its rapid improvement with iodine and thionamides.

Conclusions. Our case suggests that severe hyperbilirubinemia can be caused by hyperthyroidism and the etiology of hepatic dysfunction should include thyrotoxicosis as a probable cause. Aggressive treatment should be done with iodine and thionamides for fruition.

Keywords: hyperbilirubinemia, pregnancy, thionamides, thyrotoxicosis

Hyperthyroidism is estimated to be prevalent in 0.8–1.3% of the population, more common in women and increases with age (De Leo et al. 2016). Hepatic dysfunction is common in patients with thyrotoxicosis in the form of abnormal levels of liver enzymes occurring in 15–75% of affected individuals (Thompson et al. 1978; Biscoveanu and Hasinski 2000). Frank jaundice is rare, occurring in 5% of patients of hyperthyroidism, more common in thyroid storm and implicates a poor prognosis (Wartofsky et al. 2005; Akamizu 2018).

We present a clinical history and laboratory features of a pregnant patient whose clinical condition deteriorated with eventual slow gradual improvement on institution of antithyroid drugs and iodine. It is important to consider the thyrotoxicosis in patients with jaundice of unknown cause and consider the use of antithyroid drugs for treatment of the thyrotoxicosis associated hyperbilirubinemia.

Case Report

A 23-year-old primigravida (fifth month) female diagnosed with hyperthyroidism on irregular treatment for two years presented to us with a three-day history of new onset jaundice. Patient had a two-month history of dyspnea (NYHA II) with easy fatigability, which progressed (NYHA III) in the last one week. Associated complaints of black stools and low-grade fever were also present for the past two days. She had features of thyrotoxicosis in the form of tremors, weight loss, history of oligomenorrhea, and increased frequency of stools. No history of any prior cardiac disease or any risk factors for liver disease was found. She denied taking any ayurvedic medications. No relevant family history was present.

On physical examination, body mass index (BMI) was 17.8 kg/m^2. She was tachypneic, tachycardiac, normotensive requiring nasal oxygen support. Patient

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had severe pallor, deep icterus, bilateral pitting pedal edema with distended neck veins. Soft, diffusely enlarged, midline neck swelling moving with deglutition was present. Signs of hyperthyroidism were present. There were no signs of ophthalmopathy.

Further evaluation showed absent fetal cardiac activity, and hence termination of pregnancy was done after stabilizing the patient.

On admission, the blood workup was done as listed in Tables 1, 2, and 3.

In the following days, the condition deteriorated with development of high-grade fever, severe hypotension, and jaundice with increasing pedal edema and pulmonary edema despite treating heart failure and sepsis. Although there was no complaint of overt bleeding, patient continued to have passage of black stools and consequent drop in hemoglobin. The bilirubin continued to rise over the period of 20 days to a peak of 68.2 mg/dL (1166 μmol/L). Chest radiograph on admission showed cardiomegaly and pulmonary infiltrates. Abdominal ultrasonography showed normal liver, biliary tree, and gall bladder with no evidence of biliary obstruction. Other blood investigations showed sickling negative, lactate dehydrogenase enzyme mildly elevated and Coomb's test negative. Hepatic serologies (HbsAg, HCV, HAV, and HEV) were unrevealing. Echocardiography showed concentric left ventricular hypertrophy with mild global left ventricular hypokinesia. Neck ultrasonography showed a hypoechoic left lobe of thyroid, diffusely enlarged measuring up to 12 cm in maximum dimensions with few calcific foci. Anti-thyroid peroxidase antibodies and thyroid-stimulating hormone (TSH) receptor antibodies were absent. Above findings were suggestive of autonomous functioning nodule.

Table 1
Biochemical profile at the time of admission

Parameter	On admission	Reference interval
Creatinine (mg/dL)	1.19	0.6–1.2
Total bilirubin (mg/dL)	15.8	0.2–1.0
Direct bilirubin (mg/dL)	7.5	0.0–0.4
Indirect bilirubin (mg/dL)	8.3	0.2–0.6
AST(IU/L)	688	0–37
ALT (IU/L)	910	0–40
ALP (IU/L)	363	30–150
Sodium (mEq/L)	139	135–145
Potassium (mEq/L)	5.1	3.5–5.1

Abbreviations: AST – aspartate aminotransferase; ALT – alanine transaminase; ALP – alkaline phosphatase.

Table 2
Hemogram at the time of admission

Hemogram	On admission	Reference interval
Hemoglobin (gm/dL)	7.8	11.9–14.8
Total count (/cm^2)	10600	3800–10400
Differential count (N/L/E/M)	90/8/1/1	
Platelet count (/μL)	120000	150000–410000

Abbreviations: E – eosinophil; L – lymphocyte; M – monocyte; N – neutrophil.

Table 3
Coagulation profile at the time of admission

Coagulation profile	On admission	Reference interval
PT (Value/Control)	15.2/12.4	11–14
INR	1.28	
aPTT (Value/Control)	40.0/32.8	28–36

Abbreviations: aPTT – activated partial thromboplastin time; INR – international normalized ratio; PT – prothrombin time.

The R factor, which is used to help determine the likely type of liver injury in patients with elevated transaminases and alkaline phosphatase, was 9.42 on admission indicating hepatocellular injury and after 1 week it was 0.7989 indicating cholestasis.

$$R\ Factor = \frac{\frac{ALT}{Upper\ Limit\ of\ Normal\ of\ ALT}}{\frac{ALP}{Upper\ Limit\ of\ Normal\ of\ ALP}}$$

The R factor was interpreted as follows: ≥5 – hepatocellular injury; >2 to <5 – mixed injury; ≤2 – cholestatic injury.

The thyroid profile is shown in Table 4.

Patient was started on broad spectrum antibiotics which were stepped up as per cultures. Albumin and vitamin K were given for liver dysfunction. Patient was given several pints of red cell concentrates and fresh frozen plasma over a period of one month, where the patient had a consistent fall in hemoglobin along with passage of tarry black stools. Carbimazole was started with 20 mg and gradually escalated to 40 mg divided in three doses. Initially, propranolol (20 mg) four times a day was started. Ursodeoxycholic acid and later cholestyramine was started for pruritus. Despite being adequately treated with antithyroid drugs, managing heart failure and sepsis, bilirubin continued to rise for three weeks post admission. As per consultation with the endocrinologist, Prednisolone of 30 mg was then given for five

days along with Lugol's iodine (five drops with juice/water three times daily). Prednisolone was gradually tapered off over the next few days. Propranolol was continued. Following the initiation of Lugol's Iodine, bilirubin started to decline rapidly. Two-month post admission, bilirubin and liver profile parameters eventually reached near normal limits, which is shown in Table 5 and Figures 1–3. Patient eventually had a BMI of 14.2 kg/m^2.

Thyroidectomy was advised and she was discharged on antithyroid drugs. She remained euthyroid. A one-month post discharge, she regained some of her original weight.

Discussion

Thyrotoxicosis may be associated with various abnormalities of liver function and can be cause for profound cholestasis. Thyroid hormone concentrations are important for normal hepatic function and metabolism of bilirubin (Thomas and Croom 1987). Hyperthyroidism causes an increase in the metabolic rate, which then induces a relative decrease in blood flow to certain areas of the liver resulting in hypoxic injury. Thyroid hormones might also have a direct toxic effect on the hepatic tissue. As studied in rats, hyperthyroidism lowered the bilirubin UDP-glucuronosyltransferase activity, produced a decreased ratio of bilirubin di- to monoconjugates in bile and plasma, and a decreased ratio of conjugated to total bile pigment concentration in liver and in plasma (Van Steenbergen et al. 1988). Thus, if extrapolated

Table 4
Thyroid profile over the course of admission and treatment

Thyroid profile	On admission	Reference interval
Total T3 (ng/mL)	>8.0	0.60–1.81
Total T4 (μg/mL)	>30.0	4.5–12.6
TSH (μIU/mL)	0.014	0.55–4.78
After 2 weeks		
fT3 (pg/mL)	12.85	2.0–4.4
fT4 (ng/dL)	2.79	0.93–1.70
TSH (μIU/mL)	<0.005	0.27–4.20
After 4 weeks		
Total T4 (μg/dL)	8.81	5.1–14.1
fT4 (ng/dL)	1.94	0.93–1.70

Abbreviations: TSH – thyroid stimulating hormone; T3 – triiodothyronine; fT3 – free triiodothyronine; T4 – thyroxine; fT4 – free thyroxine.

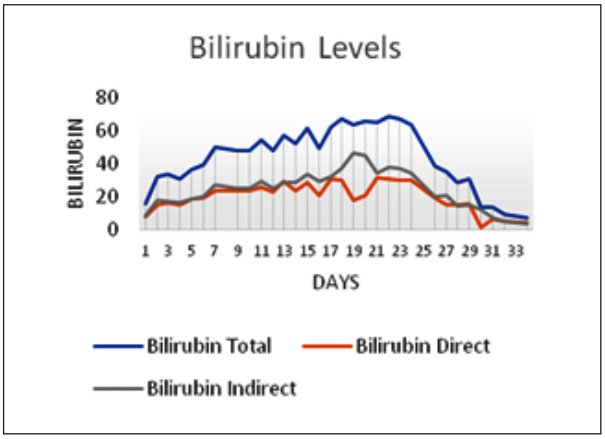

Figure 1. The trend of bilirubin levels (mg/dL) over the course of the illness.

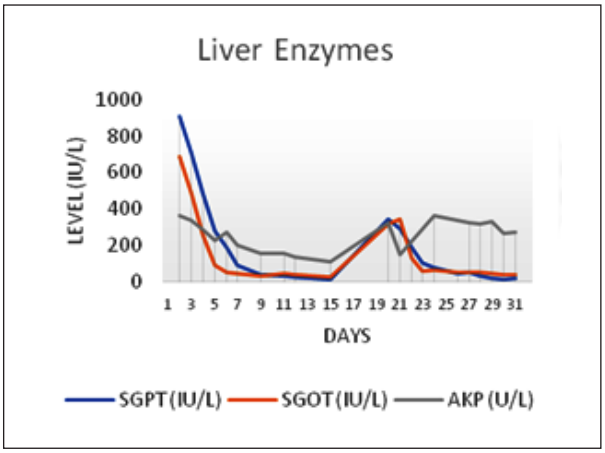

Figure 2. The trend of liver enzymes (IU/mL) variation over the course of illness. Abbreviations: AKP – alkaline phosphatase; SGOT – serum glutamic-oxaloacetic transaminase; SGPT – serum glutamic-pyruvic transaminase.

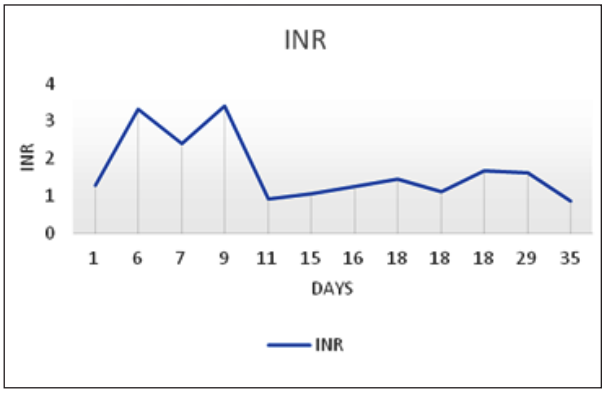

Figure 3. Prothrombin time (PT)/international normalized ratio (INR) over the course of admission. Fresh frozen plasma (FFPs) was administered as per clinical indication. The PT/INR returned to normal values with effective control of hyperthyroid status and heart failure.

Table 5
Liver profile and its progression over time

Parameter	Week 1	Week 2	Week 3	Week 4	Week 5	Week 7	Reference interval
AST(IU/L)	688	33	26	126	53	41	0–37
ALT (IU/L)	910	38	14	186	44	18	0–40
ALP (IU/L)	363	155	109	149	322	271	30–150
Total protein (mg/dl)	6.0	6.1	5.9	7.2	5.0	6.0	6.0–8.0
Albumin (mg/dl)	3.2	3.2	3.0	3.7	3.0	3.2	3.5–5.0
Bilirubin total (mg/dl)	15.8	47.9	49.3	68.2	38.4	7.1	0.2–1.0
Bilirubin conjugated (mg/dl)	7.5	23.0	20.6	30.6	19.0	3.9	0.0–0.4

Abbreviations: AST – aspartate aminotransferase; ALT – alanine transaminase; ALP – alkaline phosphatase.

in humans, it may show a slightly higher indirect bilirubin as compared to direct bilirubin, which is clearly seen in our patient. Generally, it is observed that patients with hyperthyroidism and heart failure exhibit more severe liver dysfunction (deep jaundice), hepatomegaly, ascites and coagulopathy than those without heart failure (Khemichian and Fong 2011).

We presented this case report to show that unusually high bilirubin (1166 μmol/L) can be associated with hyperthyroidism. Patient presented with fever and jaundice along with other features of hepatic dysfunction in addition to features of hyperthyroidism. This was a unique case because associated factors such as pregnancy with severe anemia, heart failure, and septicemia complicated the search for etiology for liver dysfunction. Consistent fall in hemoglobin with melena likely due to peptic ulcer, which showed underlying coagulopathy due liver dysfunction contributed by hyperthyroidism and heart failure. Treatment along the lines of congestive cardiac failure was unpromising. A common reason for jaundice in thyrotoxicosis is liver injury induced by several medications including thionamides which were started from admission (Niculescu et al. 2016). It is estimated that the incidence of antithyroid associated hepatic dysfunction is between 0.1% and 0.2% (Cooper 2005); and risk factors for hepatic injury include older age and higher doses of antithyroid medications. Thus, a clinical challenge of using drugs that cause cholestasis or hepatic injury to treat hepatic dysfunction presented to us.

The dilemma of reconsidering stopping antithyroid drugs for resolution of ever-increasing jaundice or continuing treatment and actively waiting for resolution of hyperbilirubinemia loomed over us. According to studies, Lugol's Iodine treatment decreased the rate of blood flow, thyroid vascularity and decreased thyroid hormone levels temporarily (Erbil et al. 2007; Calissendorff and Falhammar 2017; Kulkarni et al. 2021). Lugol's Iodine and its acute effect was a game changer and helped guide further management. Following initiation of iodine, clinical stability and restoration of lab values ensued. With its use, the antithyroid effect (Wolff-Chaikoff effect) (Markou et al. 2001; Hull et al. 2007) on liver indicated that the culprit of hyperbilirubinemia was thyroid storm itself and thus continuation of carbimazole was decided.

A limitation of our report is inability to do liver biopsy partly due to financial constraints and partly because our patient responded well to treatment of thyrotoxicosis.

Conclusion. An unusually high bilirubin may be associated with thyrotoxicosis in rare cases. Patients presenting with jaundice not responding to management of the common causes should be evaluated for thyrotoxicosis. Management with thionamides, steroids and iodine should be promptly initiated for thyrotoxicosis.

Conflicts of interest: *The authors declare no conflicts of interest.*

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