A 28-Year-Old Woman with Impending Thyroid Storm, Hyperbilirubinemia, and Total AV Block

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ABSTRACT

Thyrotoxicosis, a state of excess thyroid hormone, often presents with diverse clinical manifestations, including thyroid storm, a rare but critical condition. Here, we present a case of a 28-year-old woman with thyrotoxicosis, hyperbilirubinemia, and total atrioventricular (AV) block. The patient exhibited jaundice, chest discomfort, and a history of chronic diarrhea, weight loss, tremors, and exertional dyspnea. She was on propylthiouracil and propranolol for two weeks.

Physical examination revealed jaundice, proptosis, a large goiter, and tremors. Laboratory tests on admission indicated elevated liver enzymes, hypokalemia, and markedly elevated thyroid hormones. ECG revealed total AV block. Treatment involved hydrocortisone, thiamazole, discontinuation of propranolol, and gradual correction of electrolyte imbalances.

The patient improved clinically, and propranolol's discontinuation improved the rhythm disturbance. The Patient was discharged for outpatient Graves' disease management.

Future assessments may include an electrophysiology study if needed. Total AV block in thyrotoxicosis is rare. This case highlights the complexity of managing thyrotoxicosis with concurrent hepatic and cardiac complications, emphasizing the importance of tailored treatment strategies and close monitoring.

Keywords: *Graves' disease, thyroid storm, hyperbilirubinemia, total av block.*

INTRODUCTION

Thyroid hormone excess, also known as thyrotoxicosis, manifests with a range of clinical presentations and multi-system involvement. Thyroid storm accounts for about 1% to 2% of admissions for hyperthyroidism.[1] The male-to-female ratio for the incidence of thyroid storm was about 1:3.[2] Fever, tachycardia, and hypertension with neurological and gastrointestinal symptoms are the commonly encountered clinical features. Although hepatic dysfunction can be linked to a thyrotoxic crisis, it's crucial to determine

the underlying cause of jaundice and liver abnormalities, especially if drug-induced cholestasis or autoimmune liver diseases are suspected, as they require specific management strategies.[3]

Thyroxin's ability to sensitize the catecholamine receptors, causing tachyarrhythmias, is well addressed. However, thyrotoxicosis is considered one of the least common causes when it comes to the etiology of advanced heart block.[4] In this case report, we present a 28-year-old woman with thyrotoxicosis, hyperbilirubinemia, and total AV block.

CASE ILLUSTRATION

A 28-year-old woman presented with worsening jaundice and chest discomfort over the past two weeks. She reported a year-long history of chronic diarrhea, accompanied by weight loss, tremors, nausea, and exertional shortness of breath. The patient had been diagnosed with hyperthyroidism a month before admission, but faced difficulties continuing hospital treatment due to health insurance issues. Previously, she had been prescribed propylthiouracil 3x200 mg and propranolol 3x20 mg for the past two weeks.

The patient was fully alert and had a notably jaundiced appearance. She was 156 cm tall and weighed 51 kg (BMI 20.9 kg/m^2). Her blood pressure was measured at 120/80 mmHg, and she had an irregular pulse of 56 beats per minute. Notable scleral icterus was observed, along with proptosis. During thyroid examination, a large symmetrical, non-tender goiter was noted. Her abdomen exhibited mild diffuse tenderness without ascites or organomegaly. Additionally, a fine tremor was noted in the upper extremities.

The laboratory investigations conducted during the patient's hospitalization are summarized in **Table 1**. These tests revealed several noteworthy findings: On Day 1, initial laboratory evaluation demonstrated total bilirubin levels of 21.56 mg/dL (reference range 0.0-1.0), direct bilirubin levels of 16.71 mg/dL (0.0-0.30), aspartate aminotransferase (AST) levels of 54 mg/dL (15-34), alanine aminotransferase (ALT) levels of 38 mg/dL (15-60), Alkaline Phosphatase levels of 193 mg/dL (50-136), and Gamma GT levels of 40 mg/dL (5-55). Albumin levels were reduced to 3.2 g/dL (3.4-5.0). Potassium levels declined from an initial measurement of 4 mmol/L (3.5–5.1) to 2 mmol/L by Day 3, eventually rising to 5.1 mmol/L on Day 10 after intravenous correction for hypokalemia. Initially, below normal calcium levels gradually increased to 2.2 mmol/L by Day 7 following intravenous calcium gluconate administration. Free T4 was markedly elevated at 52.35 pmol/L (10.6-19.4), indicative of hyperthyroidism. However, it gradually decreased on subsequent days, measuring 41.17 pmol/L on Day 7 and 40.45 pmol/L on Day 14. Thyroid-stimulating hormone (TSH) was significantly low, measuring <0.01 uIU/mL (0.25-5.0) on Day 1, confirming the diagnosis of hyperthyroidism. Troponin I level remained within the normal range at 0.01 ug/L (0.036-0.065). Both hepatitis B surface antigen (HbsAg) and Anti-HCV tests yielded negative results.

TRAb examination showed a level of 22.35 IU/l (reference range ≤1.75), while both ANA and anti-AMA antibodies yielded negative results. The Burch-Wartofsky score reached 35 points, indicating an impending thyroid storm. Thyroid ultrasound revealed enlargement of both thyroid lobes with increased vascularity. An ECG examination on day 1 depicted a Total AV Block with a Junctional escape beat (**Figure 1**). Echocardiography confirmed normal systolic function (EF 66.5%). Abdominal ultrasound did not reveal any abnormalities in the liver or bile ducts.

The patient was administered hydrocortisone 3x100 mg, and propylthiouracil was switched to thiamazole 30-0-20 mg. Propranolol was discontinued, resulting in an improvement of the Total AV Block. Bisoprolol was initiated at a dose of 5 mg/24 hours on the third day of treatment. Additionally, the patient received Lugol's solution at 4x8 drops, calcitriol 1x0.25 mcg, ursodeoxycholic acid 2x250 mg, and calcium gluconate 1x1 ampule. Treatment for hypokalemia was also administered. The patient demonstrated gradual clinical and laboratory improvement throughout the treatment. On Day 14, the free T4 level was 40.45 pmol/L (reference range: 10.6-19.4), and the patient's symptoms had improved. Two weeks after

hospitalization, the patient was discharged with plans for definitive outpatient management of Graves' disease. The patient continued routine treatment as an outpatient and experienced clinical improvement. There were no complaints during the follow-up evaluation in January 2024, and the FT4 level was 2.43 pmol/L (10.6-19.4).

Table 1. Laboratory Evaluation

Lab Results	Normal Range	Day 1	Day 3	Day 5	Day 6	Day 7	Day 10	Day14
Total Bilirubin (mg/dL)	0,0-1,0	21.56	16,74			9.97	11,3	7,5
Direct Bilirubin (mg/dL)	0,0-0,30	16,71	10,92			5.52	8.9	6,79
AST (U/L)	15-34	**54**	**45**					
ALT (U/L)	15-60	38	38					
Alkaline Phosphatase (U/L)	50-136	**193**	**133**					
Gamma GT (U/L)	5-55	40	33					
Albumin (g/dL)	3,4-5	**3,2**						
Potassium (mmol/L)	3,5 – 5,1	4	**2**	**2,1**	**2,1**	**2,6**	**5,1**	3,9
Calcium (mmol/L)	2,12-2,52	**1,9**			**1,9**	**1,9**	2,2	
Free T4 (pmol/L)	10,6-19,4	**52,35**				41,17		40,45
TSH (uIU/ml)	0.25 - 5.0	**<0,01**						
Troponin I ug/L	0.036-0.065	0,01	0,01					
HBsAg	Negative	Negative						
Anti-HCV	Negative	Negative						

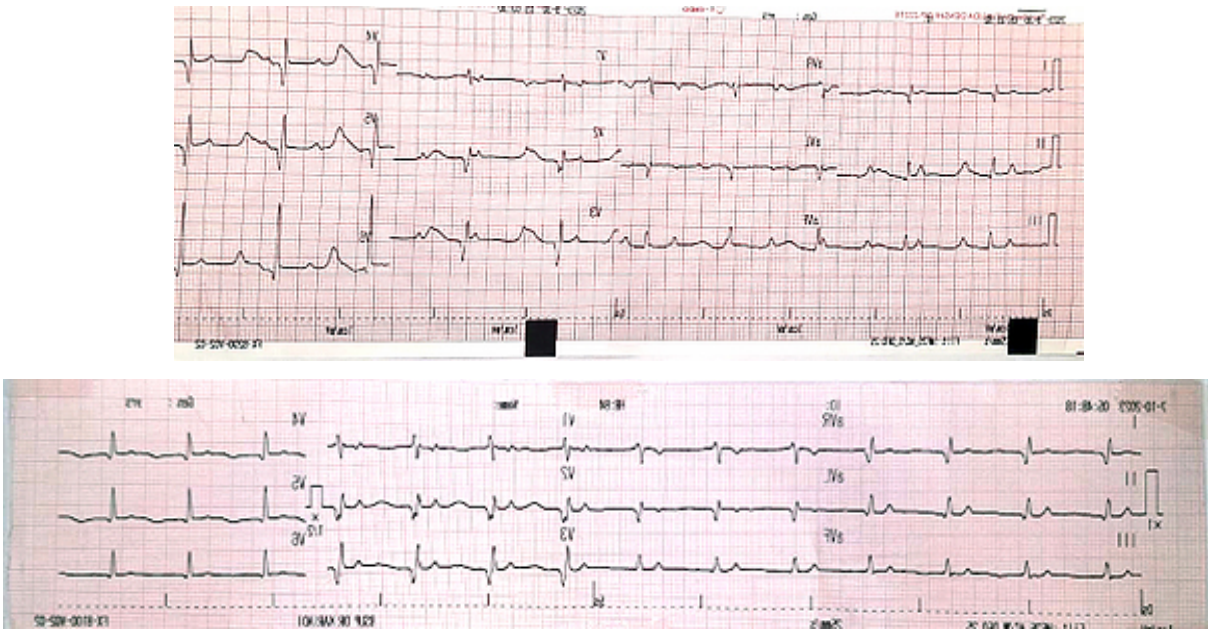

Figure 1. ECG Changes on Day 1 (Top) and Day 7 (Bottom)

DISCUSSION

A patient with Graves' disease presented with an impending thyroid storm, hyperbilirubinemia, and total AV block. Hyperbilirubinemia can be caused by the thyrotoxic crisis itself, medications used in the treatment of hyperthyroidism, autoimmune disorders such as autoimmune hepatitis (AIH) or primary biliary cholangitis, Gilbert syndrome, heart failure leading to liver congestion, or arterial embolism in the liver.[5]

Several direct and indirect mechanisms have been suggested as the cause of liver dysfunction in hyperthyroidism. Summarily, these include direct liver toxicity from prolonged exposure to excessive thyroid hormones and hepatocyte anoxia with free-radical damage as a result of the hypermetabolic state, liver cell degeneration from accelerated liver glycogen and protein decomposition, autoimmune-related liver injury, congestive hepatopathy (necrosis) from concomitant thyrotoxic heart failure, previous underlying liver disease and antithyroid medication-related liver toxicity and injury. The pattern of liver dysfunction associated with hyperthyroidism varies. In situations without heart failure and underlying autoimmune causes, elevated aspartate aminotransferase and alanine aminotransferase (transaminitis) result from tissue ischemia and infarction of the hepatocytes.[6]

Evaluation for cholestasis in patients with autoimmune thyroid disease should include searching for other autoimmune etiologies because approximately 10% of patients with Graves' disease will experience liver damage through autoimmune mechanisms. Therefore, patients with concurrent liver dysfunction and hyperthyroidism should undergo appropriate examinations for non-thyroidal autoimmune diseases.[7]

Serum protein electrophoresis in the patient revealed hypergammaglobulinemia (**Figure 2**). The possibility of autoimmune hepatitis (AIH) increases with the presence of hypergammaglobulinemia, particularly elevated serum IgG levels. However, the patient's ANA and Anti-AMA tests yielded negative results, eliminating suspicion of AIH and primary biliary cholangitis. The Simplified Diagnostic Scoring System from the International Autoimmune Hepatitis Group (Simplified AIH Score) can confirm AIH diagnosis, utilizing histopathological findings as one scoring point. If the Simplified AIH Score is ≥7, the diagnosis of AIH can be confirmed.[8] Our patient has not undergone a biopsy related to the thyrotoxicosis condition due to the associated risk of cardiac rhythm disturbances. Furthermore, although a biopsy was performed, the obtained results were insufficient to confirm an AIH diagnosis as the Simplified AIH Score remained below 7 points.

Treatment with propylthiouracil has been reported to cause elevated liver transaminases in around 30% of patients. Meanwhile, treatment with methimazole and carbimazole only leads to liver enzyme changes in a few cases[3] The mechanism behind liver injury due to propylthiouracil usage is not yet fully understood, but it's suspected to be caused by immunological reactions to its metabolites.[9] Therefore, in cases of thyroid storm accompanied by severe hyperbilirubinemia, the use of methimazole is preferred because of its milder liver toxicity.

The possibility of Gilbert syndrome was excluded because the hyperbilirubinemia in the patient predominantly involved an increase in direct bilirubin (conjugated hyperbilirubinemia). Gilbert syndrome should be suspected in individuals with unconjugated hyperbilirubinemia. Additionally, the possibility of jaundice due to liver congestion was ruled out as the abdominal ultrasound showed no abnormalities in the liver, and echocardiography confirmed normal systolic function (EF 66.5%).

Impaired AV conduction is a very rare complication of thyrotoxicosis. Bradyarrhythmias complicating hyperthyroidism have commonly been associated with acute infectious disease, hypercalcemia, thyroid storm, or underlying structural heart disease. [10] Additionally, there are reports of a relationship between hyperthyroidism and AV block, independent of antithyroid medications or other drugs given for hyperthyroidism treatment (such as beta blockers), and not contingent on the presence of concurrent illness. Other theories suggest pre-existing latent hypervagotonia by the autonomic nervous system secondary to excess thyroid

hormone in the body, thyroid hormone-induced myocarditis and associated inflammation, the possibility of a direct thyrotoxic effect on cardiac tissue, and autoimmune reaction against cardiac nodal tissue.[11]

In our patient, AV block was suspected as a side effect of propranolol, leading to its discontinuation during treatment. Myocarditis and inflammation were ruled out, as troponin levels during evaluation remained normal. Following the discontinuation of propranolol, the cardiac rhythm disturbance improved. The precise mechanism of total AV block in thyrotoxicosis remains undisclosed. Interstitial inflammation at the AV node or focal myocarditis around the AV node has been reported in a patient with hyperthyroidism. Nevertheless, an Electrophysiology Study (EPS) is planned for future assessment if the patient experiences recurrent rhythm disturbances.

The underlying mechanism for hypokalemia in this patient involves thyroid hormones stimulating Na+–K+ ATPase in skeletal muscle by increasing the transcription of genes encoding Na+–K+ ATPase and enhancing the intrinsic activity or insertion of this pump into the membrane. Therefore, it's not a pure potassium depletion in the body. Insulin, high-carbohydrate meals, and exercise are other known activators of Na+–K+ ATPase.[12]

CONCLUSION

We present a case of a patient with thyrotoxicosis due to Graves' disease who presented with hyperbilirubinemia and total AV block. The possibility of cholestasis due to autoimmune hepatitis in the patient has been ruled out. In an impending thyroid storm with cholestasis, the preference for thiamazole over propylthiouracil is due to thiamazole's lower hepatotoxicity. However, the total AV block in this case is suspected to have occurred due to the side effects of propranolol, although an electrophysiology study (EPS) remains scheduled for future assessment if the patient experiences recurrent rhythm disturbances.

CONFLICT OF INTEREST

We have no conflicts of interest to disclose. All authors declare that they have no conflicts of interest.

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