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Thyrotoxicosis-Associated Cholestatic Jaundice in a Patient With Incidental Gallstone Disease: A Case Report and Literature Review

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Patient: Female, 62-year-old
Final Diagnosis: Hyperthyroidism
Symptoms: Abdominal pain • jaundice • tachycardia • weight loss
Clinical Procedure: —
Specialty: Endocrinology and metabolic

Objective: Unusual clinical course

Background: Thyrotoxicosis is associated with well-recognized and clinically significant complications, including congestive heart failure and cardiac arrhythmias. The relationship between hyperthyroidism and hepatic dysfunction is complex, with several proposed pathophysiological mechanisms; however, direct cholestatic injury is frequently overlooked. Although mild liver enzyme elevation is common in hyperthyroidism, clinically overt jaundice is rare. Nevertheless, increasing evidence from case reports and case series suggests that thyrotoxicosis, especially Graves disease, can result in cholestatic-pattern jaundice. This temporal association is supported by substantial improvements in jaundice and liver biochemistry after antithyroid therapy.

Case Report: A 62-year-old woman presented with a 1-month history of right upper quadrant abdominal pain, unintentional weight loss, and jaundice. Laboratory evaluation demonstrated cholestatic-pattern liver injury, and abdominal ultrasound revealed a solitary gallstone without evidence of acute or chronic cholecystitis. Abdominal computed tomography demonstrated right-sided heart failure with pericardial and bilateral pleural effusions and congestive hepatopathy. Endoscopic retrograde cholangiopancreatography showed no filling defects, excluding biliary obstruction. Because the patient had persistent sinus tachycardia, thyroid function tests were performed. The findings were consistent with primary hyperthyroidism and elevated thyroid-stimulating hormone receptor antibodies); thyroid ultrasound and scintigraphy results supported toxic multinodular goiter. Treatment with methimazole led to dramatic improvement of the jaundice. Given the possibility of competing etiologies, thyrotoxicosis was considered the most likely contributing factor to cholestatic jaundice onset.

Conclusions: This case highlights the importance of considering hyperthyroidism in the differential diagnosis of jaundice, particularly in diagnostically challenging cases.

Keywords: Thyrotoxicosis • Jaundice, Obstructive • Liver Diseases

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/953338

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Introduction

Hyperthyroidism is a condition characterized by excess thyroid hormone production, leading to a state of hypermetabolism. Thyrotoxicosis is associated with various thyroid disorders, including Graves disease, toxic adenoma, multinodular goiter, thyroiditis, and treatment-related conditions (eg, iodide, amiodarone, and radiographic contrast agents) [1]. Other causes include central disorders affecting the hypothalamus or pituitary gland, as well as peripheral causes such as struma ovarii [2]. The classic presentation of thyrotoxicosis encompasses features reflecting a hypermetabolic state. Heat intolerance, tremor, anxiety, fatigue, weight loss, and palpitations are typical symptoms of hyperthyroidism [3]. Some patients may present with nonspecific or vague symptoms; thus, biochemical confirmation with thyroid function testing is essential for diagnosis [4].

Deranged liver enzymes are a well-established manifestation of thyrotoxicosis; a systematic review found that 60% of patients had at least 1 abnormal liver function test, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), bilirubin, or gamma-glutamyl transferase (GGT) [5]. The review also found that, although the available evidence did not clearly define the pattern of hepatic injury, a cholestatic pattern was evident only in case reports [5].

Cholestatic liver injury is defined as impaired bile flow into the gastrointestinal tract. Laboratory findings consistent with a cholestatic pattern include elevated direct bilirubin (hyperbilirubinemia) and serum ALP levels typically greater than 3 times the upper limit of normal, accompanied by elevated GGT levels. In contrast, aminotransferase levels are typically normal or only mildly elevated [6,7]. Cholestatic liver injury can be classified as intrahepatic (functional) cholestasis, resulting from injury to hepatocytes or the intrahepatic bile ducts, or extrahepatic (obstructive) cholestasis, which arises from obstruction of biliary drainage outside the liver in the extrahepatic biliary tract [8].

We report an unusual presentation of cholestatic liver injury occurring in the setting of thyrotoxicosis, which posed a diagnostic challenge in the presence of incidental cholelithiasis and congestive hepatopathy. Notably, the patient demonstrated dramatic improvement after initiation of thioamide therapy. Although hepatic dysfunction in thyrotoxicosis has been described, cholestatic liver injury remains a rare manifestation; limited literature addresses its diagnosis in the presence of competing hepatobiliary etiologies. The present case adds to the existing literature by highlighting the importance of considering metabolic causes before pursuing unnecessary invasive biliary procedures.

Case Report

A 62-year-old Saudi woman presented to our emergency department with intermittent mild right upper quadrant colicky pain that did not exhibit radiation. The pain was associated with fatty meals, postprandial emesis, and decreased oral intake for the preceding 2 weeks; a similar episode had occurred 1 month earlier. Further history revealed unintentional weight loss of 34 kg over 4 years, such that weight decreased from 80 kg to 46 kg. She denied excessive sweating, insomnia, fatigue, heat intolerance, diarrhea, palpitations, fine tremor, neck swelling, or B symptoms. Her family had noticed yellow discoloration of her eyes during the current illness, which had first appeared approximately 1 month before presentation. The patient had undergone abdominal ultrasound (US) 2 weeks before presentation, which demonstrated a solitary gallstone without evidence of acute cholecystitis or biliary obstruction. Her medical history was significant for bilateral knee osteoarthritis treated via total knee replacement in 2019. On examination, she was conscious, alert, and oriented, with scleral icterus and a body mass index of 24.4 kg/m^2 (height, 140 cm). She was tachycardic, with an average heart rate of approximately 120 beats/min, but was otherwise hemodynamically stable; blood pressure was 139/86 mm Hg, temperature was 37.0 °C, and oxygen saturation was 99% on room air. Abdominal examination revealed a soft, nondistended, nontender abdomen with a negative Murphy sign and no lower extremity edema.

Initial laboratory investigations demonstrated normocytic normochromic anemia (hemoglobin, 87 g/L; mean corpuscular volume, 81.4 fL), a normal white blood cell count, elevated C-reactive protein (43.5 mg/L), and cholestatic-pattern liver injury (total bilirubin, 134.6 µmol/L; direct bilirubin, 96.8 µmol/L; ALP, 313 U/L; ALT, 23 U/L; AST, 56 U/L; GGT, 121 U/L). Brain natriuretic peptide was elevated at 408 pg/mL. Electrolytes, renal function, and cardiac biomarkers were within normal limits. Repeat abdominal US demonstrated a large solitary gallstone measuring 3 cm without evidence of acute cholecystitis, intrahepatic or extrahepatic biliary ductal dilation, or common bile duct (CBD) dilation.

The patient was assessed by the gastroenterology team, and the initial working diagnosis was obstructive jaundice. Despite the absence of biliary ductal dilation on US, endoscopic retrograde cholangiopancreatography (ERCP) was performed due to persistent conjugated hyperbilirubinemia and symptomatic cholelithiasis, raising concern for occult choledocholithiasis not visualized on initial imaging. ERCP findings were unremarkable, without evidence of biliary obstruction (**Figure 1**).

Given the pronounced weight loss, alternative systemic causes (eg, malignancy) were considered. Contrast-enhanced computed tomography (CT) of the abdomen and pelvis demonstrated no suspicious mass or lymphadenopathy. Other than

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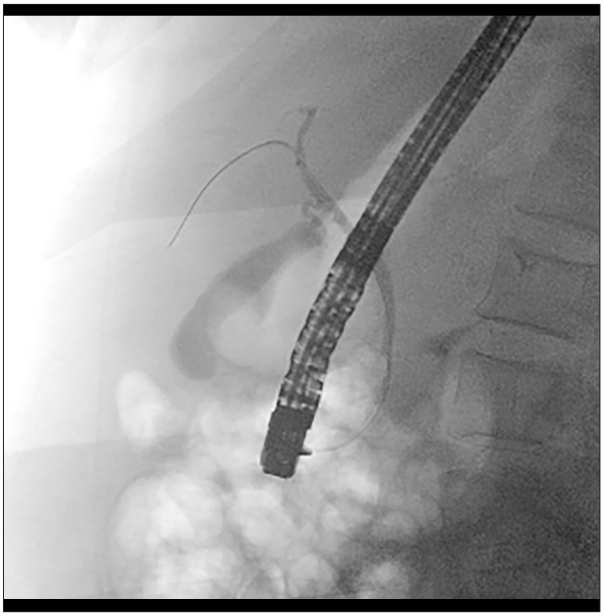

Figure 1. Endoscopic retrograde cholangiopancreatography image showing no filling defects.

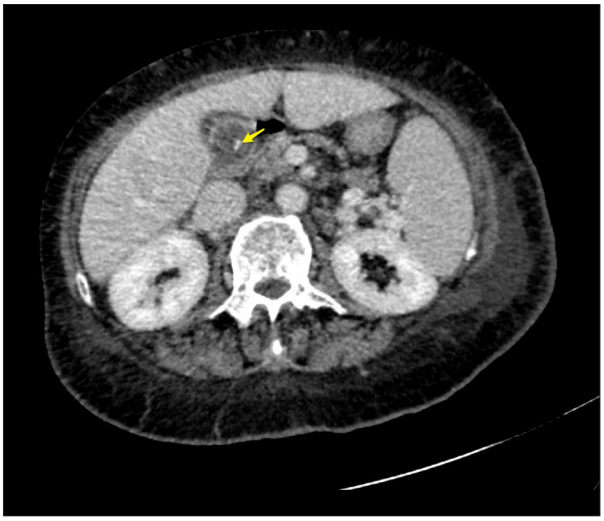

Figure 2. Abdominal computed tomography scan demonstrating a solitary gallstone (yellow arrow) without evidence of acute cholecystitis.

a solitary gallstone (**Figure 2**), there was no evidence of acute cholecystitis or intrahepatic/extrahepatic biliary ductal dilation. However, CT demonstrated findings suggestive of right-sided heart failure, including cardiomegaly, pericardial and bilateral pleural effusions, and congestive hepatopathy.

During hospitalization, the admitting team noted persistent asymptomatic tachycardia, with a heart rate ranging from 120 to 130 beats/min. Electrocardiography (ECG) and thyroid function tests were performed. ECG findings indicated sinus tachycardia with broad biphasic P waves (**Figure 3**).

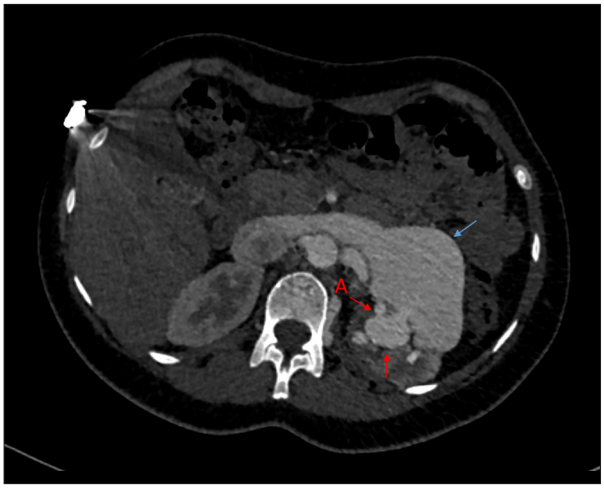

Figure 3. Electrocardiogram showing sinus tachycardia (arrows) with broad biphasic P waves (arrowheads).

Thyroid function testing confirmed thyrotoxicosis (free thyroxine [T4], 48.19 pmol/L; thyroid-stimulating hormone [TSH], < 0.01 mIU/L). Transthoracic echocardiography supported the CT findings, demonstrating a preserved left ventricular ejection fraction of 55% to 60%, moderate tricuspid regurgitation, and estimated pulmonary artery systolic pressure of 57 mm Hg.

The patient was subsequently assessed by the endocrinology team. Throughout hospitalization, she remained afebrile, fully oriented, and hemodynamically stable except for persistent tachycardia. Further investigations (**Table 1**) revealed elevated TSH receptor antibodies (38.3 IU/L; reference, ≤ 1.75 IU/L). Thyroid US demonstrated multiple bilateral nodules, and thyroid scintigraphy showed toxic multinodular goiter (**Figure 4**).

Based on these findings, the patient was diagnosed with toxic multinodular goiter in the presence of elevated TSH receptor antibodies. Her Burch-Wartofsky Point Scale score was 40, consistent with impending thyroid storm. She was admitted to a monitored bed, where she began to receive methimazole 10 mg and propranolol 10 mg. Based on the echocardiography and ECG findings, the cardiology team diagnosed cor pulmonale; furosemide was administered during hospitalization only. Thyroid US demonstrated 1 moderately suspicious nodule (TR4) and 1 mildly suspicious nodule (TR3). The management plan was to consider fine-needle aspiration if the TR4 nodule increased above 1.5 cm or the TR3 nodule increased above 2.5 cm. The patient's condition subsequently improved, and she was safely discharged home on methimazole alone.

A liver biopsy was deferred due to rapid clinical and biochemical improvement after initiation of antithyroid therapy, supporting the presumptive diagnosis.

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Table 1. Laboratory findings from admission through 2 months of medical treatment.

Investigation	Reference range	At admission	1 Week after treatment	1 Month after treatment	2 Months after treatment
Hgb	120-160 g/L	87	112	113	136
WBC	4-11 × 10^9/L	4.6	13	4.9	4.3
MCV	76-96 fL	81.4	84.1	87.3	88.4
CRP	0.1-4.9 mg/L	43.5	120	-	-
Total bilirubin	3.5-20.4 µmol/L	134.6	99.8	31.2	12.1
Direct bilirubin	≤ 8.5 µmol/L	96.8	68.6	24.2	-
ALP	39-114 U/L	313	279	274	357
GGT	10-35 U/L	121	132	244	104
ALT	6-54 U/L	23	24	33	28
AST	6-33 U/L	56	40	72	41
TSH	0.35-4.94 mIU/L	< 0.01	< 0.01	< 0.01	< 0.01
Free T4	9-19 pmol/L	48.19	20.9	9.48	10.54
Free T3	2.6-5.7 pmol/L	-	4	3.88	3.59
TSH receptor antibody	≤ 1.75 IU/L	38.3	-	34.9	-
BNP	≤ 99 pg/mL	408	1861	-	-
ANA	< 20 U	15.59	-	-	-
AMA	≤ 1: 20	< 1: 20	-	-	-
ASMA	≤ 1: 20	< 1: 20	-	-	-
Liver-kidney microsomal antibody	< 20 U	0.24	-	-	-

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AMA, antimitochondrial antibody; ANA, antinuclear antibody; ASMA, anti-smooth muscle antibody; AST, aspartate aminotransferase; BNP, brain natriuretic peptide; CRP, C-reactive protein; GGT, gamma-glutamyl transferase; Hgb, hemoglobin; MCV, mean corpuscular volume; TSH, thyroid-stimulating hormone; WBC, white blood cell count.

Two months after treatment initiation, both thyroid and liver function test results had substantially improved, with normalization of bilirubin and ALT; persistent elevation of ALP, GGT, and AST was noted. Viral serology and autoimmune workup results were negative (Table 1).

Discussion

Hepatic dysfunction is a well-recognized complication of thyrotoxicosis. Abnormal liver enzyme levels have been reported in approximately 15% to 76% of patients [8]. The relationship between thyroid function and hepatic physiology involves complex mechanisms that maintain metabolic homeostasis. Specifically, the liver plays a critical role in thyroid hormone metabolism through conversion of the inactive prohormone T4 to the active hormone triiodothyronine (T3) by type 1 deiodinase [9]. The liver also synthesizes several plasma proteins that serve as carriers for circulating thyroid hormones, including thyroxine-binding globulin, transthyretin (thyroxine-binding prealbumin), and albumin [10]. Furthermore, thyroid hormones are essential for hepatocyte growth, metabolic activity, and bilirubin metabolism [11,12]. The role of thyroid hormones in bilirubin excretion has been investigated via preclinical studies, which have shown that both hypothyroid and hyperthyroid states can alter bilirubin conjugation through effects on uridine diphosphate-glucuronosyltransferase activity, the enzyme responsible for conjugating bilirubin with glucuronic acid [13,14].

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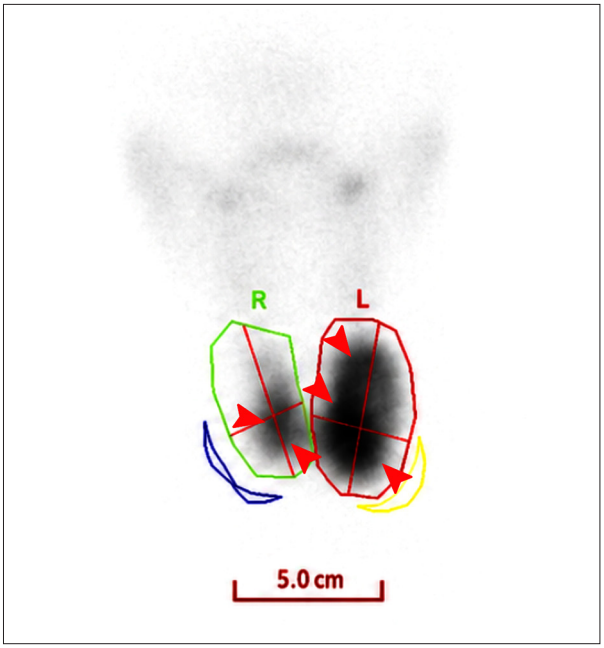

Figure 4. Technetium-99m (99mTc) thyroid scintigraphy demonstrating heterogeneous increased uptake in the right and left thyroid lobes (arrowheads), consistent with toxic multinodular goiter.

Based on this complex interaction, thyroid dysfunction, whether hypothyroidism or hyperthyroidism, can lead to liver injury through several mechanisms. Excess thyroid hormone increases hepatocyte metabolic activity. When metabolic demand exceeds hepatic blood supply, cellular hypoxia may occur, resulting in increased oxidative stress and hepatocellular injury. Thyrotoxicosis can also cause congestive hepatopathy, typically secondary to high-output heart failure. Additionally, Graves disease may coexist with autoimmune liver disorders, such as primary biliary cholangitis or autoimmune hepatitis, which should be considered during the diagnostic evaluation [8].

Cholestatic jaundice secondary to thyrotoxicosis has been described in multiple case reports and case series, as summarized in **Table 2** [15-28]. However, the underlying pathophysiology remains poorly understood. The earliest case series describing this entity was published in 1964; it involved 4 patients who developed obstructive-pattern jaundice without evidence of congestive heart failure. This observation suggested that thyrotoxicosis itself can directly affect bilirubin metabolism. The authors proposed that these patients may have had an underlying congenital or acquired defect in the intracellular conjugation or transport of bilirubin, and hyperthyroidism exacerbated the condition [29]. To our knowledge, no recent studies have systematically investigated molecular mechanisms underlying the association between thyrotoxicosis and cholestatic liver injury, despite the growing body of evidence and increasing number of published case reports concerning this clinical phenomenon.

Clinically, the presentation can be grouped into 3 main categories: constitutional, hepatobiliary, and thyroid-related manifestations. Most patients present with constitutional symptoms, including fine tremor, tachycardia, weight loss, fatigue, weakness, and anorexia. Hepatobiliary manifestations vary and may include painless jaundice or mild right upper quadrant discomfort. Pruritus, dark urine, and pale stools are also commonly reported, consistent with conjugated hyperbilirubinemia [15-29]. Thyroid-related symptoms may or may not be prominent. Some patients present with goiter, palpitations, diarrhea, and heat intolerance [20-22,25-27]. In Graves disease, ophthalmic manifestations such as exophthalmos, proptosis, lid lag, and lid retraction may also be present [18,21,22].

Congestive heart failure is a recognized complication of hyperthyroidism, although it is relatively uncommon in patients without preexisting cardiac disease. Chronic heart failure typically causes only mild elevations in liver enzyme levels, whereas acute hepatic congestion can result in pronounced enzyme elevation and hyperbilirubinemia [8]. As shown in **Table 2**, 2 case reports described the coexistence of heart failure with preserved ejection fraction and congestive hepatopathy secondary to hyperthyroidism. The patients involved also exhibited symptoms of volume overload, including dyspnea and lower extremity edema [22,24].

Regarding laboratory abnormalities, patients almost universally demonstrate findings consistent with primary hyperthyroidism, characterized by elevated free T4, elevated T3, or both, with suppressed TSH levels [30]. Graves disease constitutes the majority of reported cases [15-18,20-28], although a definitive diagnosis is not always established because TSH receptor antibody testing is not consistently reported. The 2016 American Thyroid Association guidelines state that in patients with a symmetrically enlarged thyroid gland, recent-onset orbitopathy, and moderate to severe hyperthyroidism, a diagnosis of Graves disease is highly likely and additional testing is generally unnecessary. However, when the diagnosis is uncertain, confirmation with TSH receptor antibody testing or radioactive iodine uptake is recommended [31]. In our patient, thyroid evaluation clearly demonstrated primary hyperthyroidism. Notably, thyroid US and scintigraphy findings were consistent with toxic multinodular goiter, whereas the TSH receptor antibody level was greatly elevated (38.3 IU/L; reference, ≤ 1.75 IU/L), raising suspicion for Marine-Lenhart syndrome. Marine-Lenhart syndrome is a rare form of hyperthyroidism characterized by the coexistence of Graves disease and functioning thyroid nodules, with diffuse radionuclide uptake throughout the thyroid parenchyma in addition to increased uptake in hyperfunctioning nodules [32]. Diagnostic criteria include: (a) thyroid scintigraphy demonstrating Graves disease with 1 or 2 hypofunctioning nodules; (b) increased radionuclide uptake within the nodules after TSH stimulation relative to surrounding thyroid

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Table 2. Literature review of case reports and case series of cholestasis secondary to thyrotoxicosis.

Ref	Number of patients	Sex, age	Clinical Features	Lab Findings	Radiological/ERCP Findings/Histology	Treatment	Outcomes
Hull et al (2007) [15]	2	F, 38 years	Nausea, vomiting, fatigue, jaundice, pruritus, diarrhea, weight loss, tachycardia, exophthalmos, and enlarged goiter	Borderline elevation of liver transaminases[1], elevated TB; positive hepatitis A IgM; thyroid profile consistent with primary hyperthyroidism[2] (diagnosed as Graves disease)	Abdominal US and MRCP: normal liver and biliary tree	Propylthiouracil, propranolol, dexamethasone, potassium iodide	Clinical stabilization over several days, with improvement in jaundice, pruritus, and liver biochemistry
		F, 35 years	Unconsciousness, jaundice, and goiter	Mildly elevated liver transaminases[3], elevated ALP and TB; thyroid profile consistent with primary hyperthyroidism	Liver biopsy: diffuse hepatocellular ballooning with intrahepatic cholestasis and mild portal lymphocytic infiltration. Thyroid histopathology consistent with Graves disease	β-blocker, steroids, potassium iodide, propylthiouracil, and near-total thyroidectomy	Complete recovery, with normalization of liver function tests and ALP within 3 months
Ichikawa et al (2009) [16]	1	M, 43 years	Jaundice, dark urine, pruritus, and weight loss	Borderline elevation of ALT with elevated TB and ALP; thyroid profile consistent with primary hyperthyroidism and positive TSH receptor antibodies (diagnosed as Graves disease); negative viral serology[4]	Neck US: thyroid size at the upper limit of normal. Liver biopsy: severe cholestasis involving hepatocytes and bile canaliculi with hepatocellular necrosis	Ursodeoxycholic acid, potassium iodide, methimazole	Normalization of liver enzymes and TB within 1 month
Soylu et al (2008) [17]	2	M, 47 years	Fatigue, anorexia, weight loss, pruritus, and jaundice	Predominantly direct hyperbilirubinemia with elevated ALP and GGT; thyroid profile: suppressed TSH with elevated free T3 and free T4, negative thyroid autoantibodies; negative viral serology	Normal abdominal US and MRCP. Thyroid scintigraphy: diffuse, increased technetium uptake consistent with Graves disease	Radioactive iodine	Normalization of cholestatic liver biochemistry within 3 months
		F, 67 years	Pruritus and jaundice	Normal liver transaminases with elevated GGT, ALP, and predominantly direct hyperbilirubinemia; thyroid profile consistent with subclinical hyperthyroidism, negative thyroid autoantibodies; negative viral serology	ERCP: no abnormalities. Liver biopsy: intrahepatic cholestasis	Rifampicin only	Clinical improvement, with normalization of cholestatic liver biochemistry within 2 months

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Table 2 continued. Literature review of case reports and case series of cholestasis secondary to thyrotoxicosis.

Ref	Number of patients	Sex, age	Clinical Features	Lab Findings	Radiological/ERCP Findings/Histology	Treatment	Outcomes
Regelmann et al (2012) [18]	1	F, 17 years	Jaundice, abdominal pain, pruritus, weight loss, and a painful neck mass. PE: Tachycardia (137 beats/min), exophthalmos, jaundice, melanonychia parallel to the fingernail beds, and a diffusely enlarged, nontender thyroid gland without nodules	Mildly elevated liver enzymes with elevated TB and direct bilirubin. Thyroid profile consistent with primary hyperthyroidism and positive TSI, diagnostic of Graves disease. Elevated INR. Positive hepatitis A IgM. Other serologic testing negative	Liver biopsy: Portal tracts with mild mixed inflammation and mild ductular proliferation. Hepatic lobules demonstrated diffuse hepatocellular cholestasis	Continued propranolol and methimazole. Additional treatment with ursodeoxycholic acid, rifampin, vitamin K, vitamins A, D, E, and K, and esomeprazole	Thyroid function normalized, with complete resolution of cholestasis
Breidert et al (2011) [19]	1	M, 22 years	Jaundice, abdominal cramps, and weight loss. PE: Tachycardia and pronounced jaundice	Cholestatic-pattern liver injury. Thyroid profile consistent with primary hyperthyroidism and positive TSH receptor antibodies. Negative serologic testing	Thyroid US: Increased thyroid volume with diffuse hypoechogenicity. MRCP: Normal biliary and pancreatic ducts	Thiamazole	After 2 months, normalization of thyroid and liver function with recovery of body weight
Kibirige et al (2012) [20]	1	F, 21 years	Jaundice, abdominal distension, right upper quadrant pain, exertional dyspnea, fatigue, palpitations, orthopnea, bilateral lower extremity edema, and amenorrhea. PE: Tachycardia, agitation, fever, jaundice, exophthalmos, enlarged nontender goiter, elevated jugular venous pressure, displaced and heaving apical impulse with a gallop rhythm, tender hepatomegaly, and ascites	Anemia and hypoalbuminemia. Cholestatic-pattern liver injury with elevated GGT, ALP, and direct bilirubin. Thyroid profile: Undetectable TSH with elevated free T3 and free T4	Thyroid scintigraphy: Diffuse homogeneous increased uptake, consistent with Graves disease	Carbimazole, prednisolone, propranolol, Lugol iodine, IV fluid replacement, furosemide, and captopril for heart failure	After 10 weeks, resolution of jaundice, clinically euthyroid status, and normalization of ECG, echocardiographic findings, and liver biochemistry

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Table 2 continued. Literature review of case reports and case series of cholestasis secondary to thyrotoxicosis.

Ref	Number of patients	Sex, age	Clinical Features	Lab Findings	Radiological/ERCP Findings/Histology	Treatment	Outcomes
Akande et al (2013) [21]	3	F, 27 years	Jaundice, fever, diarrhea, and vomiting. PE: Deep jaundice, fever, bilateral proptosis, tender hepatomegaly, and goiter	Predominantly conjugated hyperbilirubinemia. Thyroid profile consistent with primary hyperthyroidism	Not available	Propranolol and carbimazole	Resolution of jaundice with substantial improvement in thyroid function within 2 months
		F, 39 years	Neck swelling, fever, headache, vomiting, and jaundice. PE: Tachycardia (heart rate ≥ 120 beats/min), scleral icterus, bilateral proptosis with lid retraction, and goiter	Mildly elevated liver enzymes with conjugated hyperbilirubinemia. Thyroid profile consistent with primary hyperthyroidism	Thyroid US: Diffuse enlargement of both thyroid lobes with homogeneous echotexture and no nodules or calcifications, consistent with Graves disease. Abdominal US: No abnormalities	Propranolol and carbimazole	Clinically significant improvement with resolution of jaundice within 2 months
		F, 29 years	Neck swelling, weight loss, jaundice, and palpitations. PE: Deep jaundice, fever, bilateral proptosis with lid lag and lid retraction, and nontender goiter	Mildly elevated liver enzymes with conjugated hyperbilirubinemia. Thyroid profile consistent with primary hyperthyroidism	Not available	Propranolol, carbimazole, and supportive treatment for liver failure	Clinical improvement with resolution of jaundice within 3 weeks
Wickrama-singhe et al (2016) [22]	1	M, 35 years	Fever, jaundice, diarrhea, palpitations, bilateral ankle swelling, shortness of breath, agitation, and tremor. PE: Tachycardia with an irregular pulse, exophthalmos, and diffusely enlarged thyroid gland	Leukopenia and thrombocytopenia. Borderline elevated AST with predominantly direct hyperbilirubinemia. Thyroid profile consistent with primary hyperthyroidism and positive TSH receptor antibodies (diagnosed as Graves disease). Negative viral serology	Thyroid US: Diffuse enlargement of the thyroid gland. Echocardiography: Global cardiac dysfunction with EF of 50%	High-dose oral carbimazole, IV hydrocortisone, oral bisoprolol, IV cefuroxime, and oral clarithromycin	Normalization of liver enzymes and bilirubin within 14 days

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Table 2 continued. Literature review of case reports and case series of cholestasis secondary to thyrotoxicosis.

Ref	Number of patients	Sex, age	Clinical Features	Lab Findings	Radiological/ERCP Findings/Histology	Treatment	Outcomes
Yan et al (2017) [23]	1	M, 35 years	Painless jaundice, pruritus, acholic stools, dark urine, fatigue, exertional weakness, hand tremor, and weight loss. PE: Tachycardia, hypertension, and symmetrical thyroid enlargement	Mildly elevated liver transaminases with elevated ALP and TB and direct bilirubin. Thyroid profile consistent with primary hyperthyroidism and positive TSI (diagnosed as Graves disease)	Thyroid US: Symmetrically enlarged, hypervascular, heterogeneous thyroid gland. Abdominal CT and MRCP: No biliary ductal dilation, pancreatic or biliary mass, intrahepatic mass, or portal vein thrombosis. Liver biopsy: Acute cholestatic hepatitis with occasional single-cell hepatocyte necrosis	Atenolol, dexamethasone, cholestyramine, iodinated contrast, potassium iodide (after 72 hours), methimazole (after normalization of liver function tests), followed by thyroidectomy several weeks later	Resolution of coagulopathy and jaundice with normalization of liver function tests
Abebe et al (2018) [24]	1	M, 45 years	One-week history of generalized abdominal pain, jaundice, dark urine, and lower extremity edema. PE: Scleral icterus, proptosis, large symmetrical nontender goiter with an audible bruit, and an irregularly irregular pulse	Anemia, thrombocytopenia, hyponatremia, and acute kidney injury. Cholestatic-pattern liver injury. Thyroid profile consistent with primary hyperthyroidism and positive TSH receptor antibodies. ECG: Atrial fibrillation	Thyroid US: Enlarged heterogeneous hypervascular thyroid without nodules, consistent with Graves disease. ERCP: Normal-caliber CBD and common hepatic duct with normal intrahepatic ducts; no filling defects, strictures, or stenosis	Diltiazem, hydrocortisone, propylthiouracil, methimazole, digoxin, and metoprolol	Two weeks after discharge, bilirubin levels had improved
Barra et al (2020) [25]	1	M, 26 years	Weight loss, palpitations, progressive jaundice, choluria, and generalized pruritus. PE: Sinus tachycardia, fine tremor, warm skin, and Graefe sign	Mixed-pattern liver injury with predominantly direct hyperbilirubinemia. Thyroid profile consistent with primary hyperthyroidism and positive TSH receptor antibodies	MRCP: No cholelithiasis or choledocholithiasis. Thyroid US: Small diffuse goiter with increased vascularity, consistent with Graves disease	Propranolol, dexamethasone, cholestyramine, and RAI	Ten weeks after RAI, the patient was euthyroid with normal bilirubin and liver function tests
Rane et al (2021) [26]	1	M, 36 years	Jaundice, dark urine, pruritus, watery diarrhea, and unintentional weight loss. PE: Underweight, pallor, scleral icterus, proptosis, excoriation marks, and fine tremor	Mixed-pattern hyperbilirubinemia. Thyroid profile consistent with primary hyperthyroidism and positive anti-thyroid peroxidase (anti-TPO) antibodies (diagnosed as Graves disease)	Abdominal US: Mild hepatomegaly and gallbladder sludge with a normal biliary tree. MRCP: No abnormalities other than gallbladder sludge. Liver biopsy: Cholestasis, mild periportal inflammation, and hepatocellular ballooning degeneration	Carbimazole and propranolol	After 2 months, the patient was clinically asymptomatic, had gained weight, and demonstrated normalization of liver function tests and free T4

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Table 2 continued. Literature review of case reports and case series of cholestasis secondary to thyrotoxicosis.

Ref	Number of patients	Sex, age	Clinical Features	Lab Findings	Radiological/ERCP Findings/Histology	Treatment	Outcomes
Ajwah et al (2023) [27]	1	M, 22 years	Shortness of breath, palpitations, jaundice, pruritus, dark urine, and weight loss. Physical examination: Mild right upper quadrant tenderness	Cholestatic-pattern liver injury. Thyroid profile consistent with primary hyperthyroidism and positive TSH receptor antibodies (diagnosed as Graves disease). Hypercalcemia with suppressed parathyroid hormone. ECG: Atrial fibrillation. Negative viral serology	Technetium-99m (99mTc) thyroid uptake scan: Increased uptake (19.2%). Abdominal US: Parenchymal liver disease without biliary dilation; normal CBD and gallbladder. MRCP: Normal CBD and intrahepatic and extrahepatic bile ducts	Daily methimazole and atenolol	One month later, the patient was asymptomatic, had gained weight, and demonstrated normalization of T3 and T4 levels with improvement in bilirubin levels
Chakor et al (2025) [28]	1	M, 33 years	Jaundice, generalized pruritus for 1 month, and weight loss over 2 months. PE: Tachycardia (105 beats/min)	Borderline elevation of liver enzymes with elevated GGT, ALP, and direct hyperbilirubinemia. Thyroid profile consistent with primary hyperthyroidism and positive TSH receptor antibodies. Negative viral and autoimmune serology	Thyroid US: Diffuse, homogeneous, hypervascular goiter, consistent with Graves disease. MRCP: No dilation of intrahepatic or extrahepatic bile ducts. Liver biopsy: Cholestatic hepatitis	Carbimazole 10 mg once daily and propranolol 40 mg once daily	Resolution of jaundice and pruritus, with a 5-kg weight gain and normalization of thyroid and liver function tests

[1] Borderline elevation of liver enzymes: ALT or AST < 2 × ULN. [2] Primary hyperthyroidism: Suppressed TSH with elevated thyroid hormone levels (free T4, free T3, or both). [3] Mild elevation of liver enzymes: ALT or AST 2-5 × ULN (based on the 2017 American College of Gastroenterology guidelines). [4] Serologic testing was variably reported and, when available, included viral hepatitis and autoimmune liver disease panels; some studies reported a comprehensive autoimmune workup.
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CBD, common bile duct; CT, computed tomography; ECG, electrocardiogram; EF, ejection fraction; ERCP, endoscopic retrograde cholangiopancreatography; F, female; GGT, gamma-glutamyl transferase; INR, international normalized ratio; IV, intravenous; M, male; MRCP, magnetic resonance cholangiopancreatography; PE, physical examination; RAI, radioactive iodine; T3, triiodothyronine; T4, thyroxine; TB, total bilirubin; TSH, thyroid-stimulating hormone; TSI, thyroid-stimulating immunoglobulin; ULN, upper limit of normal; US, ultrasound.

tissue; (c) restoration of nodular function after endogenous or exogenous TSH stimulation; and (d) benign histopathology of the nodules, most commonly adenomas [33,34]. In the present case, thyroid scintigraphy demonstrated toxic multinodular goiter with distinct hyperfunctioning nodules, rather than the diffuse increased uptake characteristic of Graves disease. Thus, the patient did not meet established diagnostic criteria for Marine-Lenhart syndrome. Nevertheless, because she had positive autoimmune antibodies in addition to imaging findings consistent with multinodular goiter, we hypothesize that Graves disease developed in the setting of preexisting multinodular goiter, making this case particularly unusual.

A cholestatic pattern of liver injury, defined by elevations in ALP, GGT, and conjugated bilirubin out of proportion to AST and ALT [35], has been observed in nearly all reported cases and was also present in our patient. Our patient had a normal ALT level with only mildly elevated AST. Despite this characteristic pattern, patients presenting with cholestatic liver injury should be systematically evaluated for other potential etiologies, as summarized in **Table 3** [36]. According to the 2017 American College of Gastroenterology guidelines, patients with elevated conjugated bilirubin should undergo a thorough medication review to exclude drug-induced liver injury and abdominal US to evaluate potential biliary ductal dilation. If ductal dilation is present, magnetic resonance cholangiopancreatography (MRCP) or ERCP should be performed to assess potential biliary obstruction and other causes, including primary sclerosing cholangitis. In the absence of ductal dilation, serologic tests should include antimitochondrial antibody, antinuclear antibody, and anti-smooth muscle antibody. If the diagnosis remains inconclusive after imaging and

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Table 3. Etiologies of conjugated hyperbilirubinemia [36].

Intrahepatic causes	Extrahepatic causes
Viral hepatitis	Choledocholithiasis
Alcohol-associated liver disease	Biliary stricture
Nonalcoholic steatohepatitis	Biliary-vascular fistula
Drug-induced liver injury	Biliary atresia
Sepsis	Cholangitis (bacterial, primary sclerosing, or secondary sclerosing)
Autoimmune liver disease	Choledochal cysts
Ischemic hepatitis	Chronic pancreatitis
Hepatic storage diseases	Gallbladder carcinoma
Intrahepatic benign or malignant mass lesions	Cholangiocarcinoma
	Pancreatic tumors
	Infections

serologic evaluation, liver biopsy is recommended [37]. In our patient, serologic testing for autoimmune hepatitis and primary biliary cholangitis revealed negative findings; thus, the American College of Gastroenterology algorithm would have supported liver biopsy. However, liver biopsy was deferred due to rapid clinical and biochemical improvement after initiation of antithyroid therapy, supporting the presumptive diagnosis.

Medical management with antithyroid drugs and beta-blockers has been shown to effectively resolve cholestatic jaundice; substantial improvement in liver biochemistry was reported in several cases. This improvement also was observed in our patient, who improved with methimazole and propranolol without requiring radioactive iodine therapy or surgery. Patients with concomitant heart failure should receive guideline-directed heart failure therapy, including loop diuretics and angiotensin-converting enzyme inhibitors, as appropriate. In selected cases, particularly when antithyroid medications are contraindicated or poorly tolerated, radioactive iodine therapy or thyroidectomy (near-total or total) may be effective alternative treatment options.

The principal diagnostic challenge in the present case was identifying the primary cause of the patient's abnormal liver biochemistry, particularly the elevations in ALP and bilirubin. After exclusion of mechanical biliary obstruction, viral hepatitis, and autoimmune liver disease, 3 potential etiologies remained. First, the patient may have had congestive hepatopathy secondary to heart failure, itself a recognized complication of thyrotoxicosis. Classically, congestive hepatopathy is characterized by mild elevations in liver transaminases (typically 2-3 times the upper limit of normal), normal or minimally elevated ALP, and predominantly unconjugated hyperbilirubinemia, whereby total bilirubin rarely exceeds 3 mg/dL [38]. In contrast, our patient demonstrated predominantly conjugated hyperbilirubinemia, greatly elevated ALP, and near-normal transaminase levels, making isolated congestive hepatopathy less consistent with the observed biochemical pattern.

The second possibility was transient extrahepatic biliary obstruction due to spontaneous passage of a CBD stone. This condition is typically associated with elevations in transaminases, GGT, ALP, and direct bilirubin, along with either CBD dilation on abdominal ultrasound or intrahepatic/extrahepatic biliary dilation on MRCP. A characteristic feature is spontaneous resolution of jaundice and normalization of liver biochemistry with conservative management alone [39,40]. In our patient, however, repeated imaging demonstrated no biliary dilation; the jaundice persisted for more than 1 month prior to initiation of antithyroid therapy, arguing against a transient obstructive process. This observation is consistent with our literature review findings, in which clinical and biochemical improvement generally followed thyroid-directed treatment.

Our case was further complicated by the coexistence of several potential contributing factors, including gallstone disease, right-sided heart failure, and thyrotoxicosis. Although transient biliary obstruction could not be completely excluded, the pronounced clinical and biochemical improvement in liver and thyroid functions after initiation of antithyroid therapy strongly supports thyrotoxicosis as a major contributor to the cholestatic-pattern liver injury. Given the presence of multiple potential etiologies, we believe the hepatic dysfunction was most likely multifactorial, resulting from the direct effects of thyrotoxicosis and from congestive hepatopathy secondary to thyrotoxicosis-induced high-output heart failure.

This report not only describes a case of thyrotoxicosis complicated by cholestatic jaundice but also highlights the diagnostic challenges posed by multiple competing etiologies. Careful assessment of the temporal relationship between thyroid dysfunction and hepatic abnormalities may help guide appropriate management while avoiding unnecessary invasive investigations and procedures.

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Conclusions

Careful history taking and physical examination are essential and often provide important diagnostic clues. In the present case, persistent sinus tachycardia and substantial weight loss prompted further evaluation, ultimately leading to the diagnosis of primary hyperthyroidism complicated by congestive heart failure with elevated brain natriuretic peptide. Other clinical features that may raise suspicion include heat intolerance, palpitations, agitation, sweating, weight loss, goiter, and orbitopathy. Although the rapid biochemical improvement after initiation of antithyroid therapy suggests that thyrotoxicosis contributed to the observed hepatic dysfunction, concomitant congestive hepatopathy secondary to heart failure likely also played an important role. Thus, clinicians should consider hyperthyroidism in the differential diagnosis of unexplained cholestatic jaundice, even in the presence of other potential surgical causes, particularly when clinical features suggestive of thyrotoxicosis are present. In many cases, careful clinical assessment alone may be sufficient to raise suspicion for primary hyperthyroidism and its hepatic complications. Despite the accumulation of case reports supporting an association between thyrotoxicosis and cholestatic jaundice, higher-quality evidence is needed to establish a causal relationship and further clarify the underlying mechanisms.

Institution Where Work Was Done

Prince Mohammed Bin Abdulaziz Hospital, Medina, Saudi Arabia

Patient Consent

Informed consent was obtained from the patient for publication of this report.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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