

Challenges in early identification of causes and treatment of cholestasis in patients with hyperthyroidism: a case report and literature review

Journal of International Medical Research
48(3) 1–11

© The Author(s) 2019

Article reuse guidelines:

sagepub.com/journals-permissions

DOI: 10.1177/0300060519891018

journals.sagepub.com/home/imr



Baimei Zeng*, Ling Yuan*, Jun Chu,
Yanqing Yang and Shide Lin 

Abstract

Early identification of the causes of cholestasis is important for appropriate management of patients with hyperthyroidism. We report a patient who had hyperthyroidism and severe cholestasis after methimazole (MMI) treatment. The patient was diagnosed as having MMI-induced cholestatic hepatitis. Treatment with MMI was stopped at admission to hospital. However, his serum total bilirubin (TBil) level rose from 410.5 $\mu\text{mol/L}$ to 519.9 $\mu\text{mol/L}$ and prothrombin time activity (PTA) dropped from 81.0% to 52.2% in 10 days. To prevent further deterioration of his liver function, plasma exchange was performed three times, and dexamethasone (10 mg, intravenously) was used each time. His PTA rose to 101% and his TBil continued to increase to 669.8 $\mu\text{mol/L}$ after plasma exchange. He was subsequently diagnosed as having thyrotoxicosis-induced cholestasis and treated with radioactive iodine (380 MBq) 2 weeks after admission. His hyperthyroidism was significantly relieved, but the TBil level further increased to 776.8 $\mu\text{mol/L}$. Three weeks after admission, oral prednisone (30 mg/day) was used in this patient. Subsequently, his TBil levels gradually decreased and his liver function almost normalized within 3 months. We discuss the literature on cholestasis in the context of hyperthyroidism.

Department of Infectious Diseases, Affiliated Hospital of Zunyi Medical University, Zunyi, Guizhou, China

*These authors contributed equally to this work

Corresponding author:

Shide Lin, Department of Infectious Diseases, Affiliated Hospital of Zunyi Medical University, 201 Dalian street, Zunyi 563003, Guizhou Province, China.
Email: Linshide6@hotmail.com



Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative

Commons Attribution-NonCommercial 4.0 License (<https://creativecommons.org/licenses/by-nc/4.0/>) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (<https://us.sagepub.com/en-us/nam/open-access-at-sage>).

Keywords

Hyperthyroidism, methimazole, cholestatic hepatitis, glucocorticoid, radioactive iodine, total bilirubin

Date received: 2 July 2019; accepted: 24 October 2019

Introduction

Hyperthyroidism is a common clinical syndrome in which the thyroid produces and releases excess thyroid hormones. The most common cause of hyperthyroidism is Graves' disease. The treatment for hyperthyroidism includes surgery, antithyroid drugs (ATDs), and radioiodine therapy. Methimazole (MMI) and propylthiouracil (PTU) as oral ATDs are widely used to treat hyperthyroidism. Liver injury is a common complication in patients with hyperthyroidism.^{1,2} Severe cholestasis—either induced by thyrotoxicosis or as an adverse effect of ATD—has been increasingly reported in patients with hyperthyroidism.^{3–6} Additionally, patients with Graves' disease may also have concomitant complications in the form of other autoimmune diseases, such as autoimmune hepatitis⁷ and primary biliary cirrhosis,⁸ which can also present as cholestasis. Therefore, identification of the causes of cholestasis is important for appropriate management of patients with hyperthyroidism. We report here a patient with cholestasis and provide a brief review on the diagnosis and treatment of cholestasis in patients with hyperthyroidism.

Case report

A 41-year-old man had taken MMI intermittently since he was diagnosed with Graves' hyperthyroidism 6 years previously. Ten days before admission to hospital on 16 December 2015, he had scleral icterus

and passed dark urine after taking MMI (30 mg/day) intermittently for 2 months. One week before admission, an ultrasound scan of the neck showed diffuse enlargement of the thyroid gland with no nodules. Thyroid-stimulating hormone receptor antibodies were positive with a titer of 5.18 U/L (positive >1.75 U/L).

On admission, he had nausea, fatigue, vomiting, agitation, tremulousness, and abdominal pain. A physical examination showed that his temperature was 36.3°C and blood pressure was 119/85 mmHg. He had severe icterus of the sclerae and skin. Additionally, his thyroid was diffusely enlarged. However, his respiratory and cardiovascular systems were normal, with a heart rate of 100 beats/minute, and an abdominal examination was unremarkable. Results of the patient's blood biochemical indicators are shown in Table 1.

To exclude other causes of liver injury, additional studies showed that the patient was negative for immunoglobulin M antibodies for Epstein–Barr virus and hepatitis A and E viruses. Tests for hepatitis B virus surface antigen and core antibody, and hepatitis C virus antibody were negative. Tests for antinuclear antibody, double-stranded DNA antibody, anti-liver-kidney microsomal antibody, anti-smooth muscle antibody, and anti-mitochondrial antibody M₂ were also negative. The patient's serum ceruloplasmin level was normal. The patient also had no history of liver disease. Abdominal ultrasonography, which was performed on admission, showed unremarkable changes

of the liver, pancreas, and spleen, and no evidence of lithiasis in the common bile duct or gallbladder. Furthermore, magnetic resonance cholangiopancreatography on post-admission day 2 did not show any evidence of lithiasis, strictures, or masses in the bile duct. The patient refused to undergo percutaneous liver biopsy. The patient had no medical history, except for hyperthyroidism, and had never consumed alcohol.

After admission, because the Roussel Uclaf Causality Assessment Method (RUCAM) scale score for MMI was 7 in our patient, he was diagnosed as having MMI-induced liver injury. The R-value (alanine aminotransferase [ALT]/upper limit of normal value (ULN)/alkaline phosphatase [ALP]/ULN) in this patient was 0.667, which indicated cholestatic hepatitis. Treatment with MMI was stopped at the time of admission. The patient received standard conservative therapy, including bed rest, nutritional and energy supplements, and intravenous infusion of water-electrolyte and acid-base equilibrium maintenance. Propranolol therapy was used to

relieve his symptoms. His serum total bilirubin (TBil) level rose from 410.5 to 519.9 $\mu\text{mol/L}$ and prothrombin time activity (PTA) dropped from 81.0% to 52.2% in 10 days. To prevent further deterioration of his liver function, plasma exchange was performed three times, and dexamethasone (10 mg, intravenously) and 2000 to 2500 mL of frozen plasma was used each time. No hepatic encephalopathy was found. After plasma exchange, his PTA rose to 101%; however, his TBil level continued to increase to 669.8 $\mu\text{mol/L}$.

Assuming that thyrotoxicosis could also cause liver injury, we added radioactive iodine treatment (380 MBq) to control his hyperthyroidism 2 weeks after admission. His hyperthyroidism was greatly relieved after radioactive iodine therapy (Figure 1), but the TBil level further increased to 776.8 $\mu\text{mol/L}$ (Figure 2). Three weeks after admission, oral prednisone (30 mg/day) was administered to this patient, and his TBil level gradually decreased. The dosage of prednisone was gradually tapered (Figure 1). His liver function almost

Table 1. Laboratory findings of the patient with hyperthyroidism at the time of admission.

Laboratory variables	On admission	On discharge	Normal range
ALT (U/L)	87	38	9–50
AST (U/L)	71	39	15–40
ALP (U/L)	326	128	45–125
GGT (U/L)	32	94	10–60
TBil ($\mu\text{mol/L}$)	410.5	44.5	5–21
PTA (%)	81	126	70–150
INR	1.64	0.8	0.85–1.5
WBC ($10^9/\text{L}$)	7.08	4.35	3.5–9.5
PLT ($10^9/\text{L}$)	314	218	100–300
Cr ($\mu\text{mol/L}$)	43	48	41–109
TSH ($\mu\text{IU/mL}$)	0.003	0.009	0.5–4.8
FT3 (pmol/L)	18.1	3.7	3.5–6.5
FT4 (pmol/L)	72.9	19.4	11.5–22.7

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma glutamyl transpeptidase; TBil, total bilirubin; PTA, prothrombin time activity; INR, international normalized ratio; WBC, white blood cells; PLT, platelets; Cr, creatinine; TSH, thyroid-stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine.

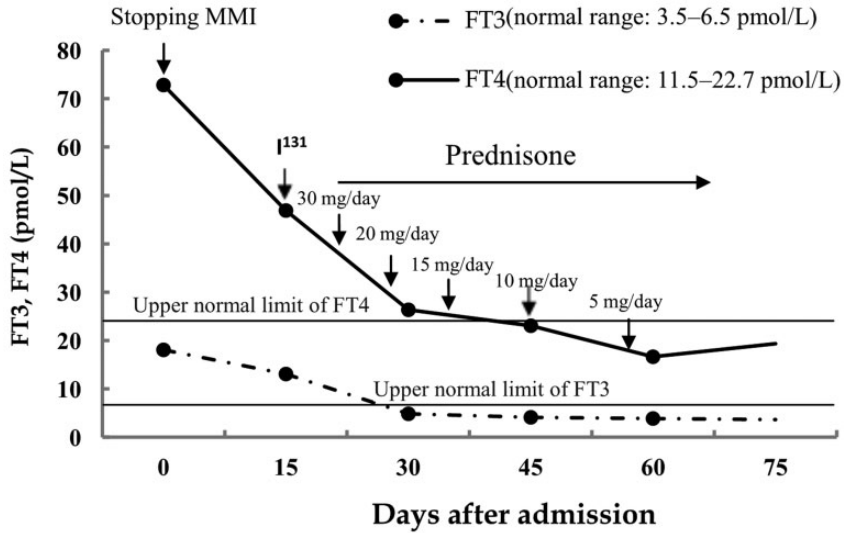


Figure 1. FT3, FT4, and TSH levels over time (days) after the patient's admission. FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid-stimulating hormone; I^{131} , radioactive iodine therapy; MMI, methimazole.

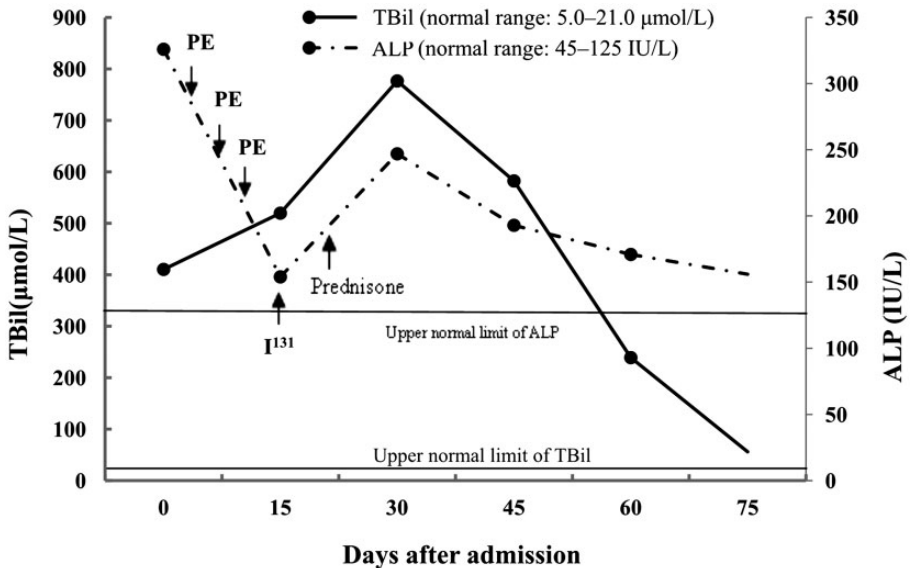


Figure 2. TBil and ALP levels over time (days) after admission of the patient. TBil, total bilirubin; ALP, alkaline phosphatase; I^{131} , radioactive iodine therapy; PE, plasma exchange.

normalized after 3 months. During the follow-up period 3 months after discharge, the patient remained asymptomatic and showed no evidence of ongoing hepatitis or sequelae.

This case report did not require ethics committee approval because it did not involve animal or human studies. Written informed consent for publication was obtained from the patient.

Discussion

Cholestasis in patients with hyperthyroidism is a rare, but complicated, severe disease. Severe cholestasis may progress to liver dysfunction and require urgent and accurate management. However, in clinical practice, identifying the causes of cholestasis in patients with hyperthyroidism is difficult.

Previous studies have shown a wide range in the incidence of abnormalities of liver function in patients with untreated hyperthyroidism. The most common abnormality of liver function is an increase in ALP levels.^{1,9} However, bone isoenzyme of ALP is responsible for an elevation in ALP levels in patients with hyperthyroidism.¹⁰ Elevation of gamma glutamyl transpeptidase (GGT) levels varies from 14% to 62% in patients with hyperthyroidism.^{11,12} Therefore, the true prevalence of cholestasis in patients with hyperthyroidism remains unknown. Severe cholestasis and liver failure have been increasingly reported in case reports of thyroid disorders^{4,5,13–19} (Table 2). A recent study showed that 65% of patients with Graves' hyperthyroidism were associated with different degrees of hepatic dysfunction. Among them, 32.4% were classified as the bile stasis type, and severe liver injury (defined as ALT or aspartate aminotransferase levels ≥ 20 ULN, GGT levels ≥ 10 ULN, ALP levels ≥ 5 ULN, and/or Tbil, direct bilirubin (DBil) levels ≥ 5 ULN) found in 6.6%

of patients before ATD treatment.⁹ Although, initially, serum thyroid-stimulating hormone levels ≤ 0.02 mIU/L were found to be a risk factor for abnormal liver biochemistry,¹ other studies showed that the severity of hyperthyroidism was not associated with the occurrence of liver injury.²⁰ Additionally, intrahepatic cholestasis has been found in patients with subclinical hyperthyroidism.²¹ The mechanisms involved in development of cholestasis in patients with hyperthyroidism are not fully understood.^{22,23} Cholestasis is related to hyperthyroidism complicated by congestive heart failure. However, cholestasis is also found in patients with uncomplicated hyperthyroidism.¹³ Other studies have suggested that increased hepatic oxygen consumption without a parallel increase in hepatic blood flow in the hypermetabolic state of hyperthyroidism may result in insufficient oxygen supply in the centrilobular zones, which may interfere with bile transport and result in cholestasis.²⁴ Recent studies have shown that hyperthyroidism increases mitochondrial oxygen consumption and production of free oxygen radicals. Oxidative stress of hepatocytes results in apoptosis of hepatocytes.^{25,26}

PTU and MMI can induce liver injury in 0.1% to 0.2% of patients with hyperthyroidism.^{27–29} Previous studies showed that PTU mostly caused hepatocellular injury and MMI often caused cholestasis.^{27,30} However, the incidence of MMI-induced cholestasis varies among reports.^{28,30,31} In a study that included 37,370 patients with hyperthyroidism treated with MMI, cholestasis occurred at a rate of 0.24/1000 person-years.²⁹ A recent study showed that in patients with ATD-induced severe hepatotoxicity, the frequency of the cholestatic type in the MMI group (35.3%) was higher than that in the PTU group (17.9%).³² Severe liver injury or severe cholestasis induced by MMI is also being increasingly reported in case reports.^{33–37}

Table 2. Previous case reports of thyrotoxicosis-induced severe cholestasis.

Authors	Patients (M or F/years)	Laboratory data	Treatment	Outcome
Yan LD, et al. ¹⁹	M/35	TBil, 15.4 mg/dL ALT, 270 U/L ALP, 379 U/L TSH, <0.01 μ IU/mL	Dexamethasone, cholestyramine, and potassium iodine	Recovered within 2 weeks
Regelmann MO, et al. ⁵	F/19	TBil, 418.9 μ mol/L ALT, 125 U/L GGT, 53 U/L TSH, 0.13 μ IU/mL	Propranolol, prednisone, and methimazole	Recovered within 1 month
Ichikawa H, et al. ¹⁷	M/43	TBil, 292.4 μ mol/L ALT, 64 U/L ALP, 488 U/L TSH, <0.01 μ IU/mL	Methimazole, potassium iodide, and ursodeoxycholic acid	Recovered within 1 month
Viallard JF, et al. ¹³	M/65	TBil, 89.0 μ mol/L ALT, normal ALP, 256 U/L TSH, undetectable	Carbimazole	Recovered within 1 month
Majeed M, et al. ¹⁴	M/28	TBil, 40.4 mg/dL ALT, 51 U/L ALP, 227 U/L TSH, <0.03 μ IU/mL	Became worse with methimazole; recovered after lithium and radioactive iodine	Recovered within 2 months
Hull K, et al. ¹⁵	F/38 F/35	TBil, 18.3 mg/dL ALT, 115 U/L ALP, normal TSH, <0.01 mIU/L TBil, 30.0 mg/dL ALT, mild elevation ALP, 263 U/L TSH, <0.01 mIU/L	Propylthiouracil, propranolol, dexamethasone, and thyroidectomy Propylthiouracil, steroids, potassium iodide, and thyroidectomy	Recovered within 1 month Recovered within 3 months
Soysal D, et al. ¹⁶	M/49	TBil, 19.7 mg/dL ALT, 100 U/L ALP, 192 U/L TSH, 0.001 IU/L	Methimazole, propranolol, and thyroidectomy	Recovered within 1 month
Kibirige D, et al. ¹⁸		TBil, 233.2 μ mol/L ALT, 17.9 U/L ALP, 212 U/L TSH, <0.005 μ IU/mL	Carbimazole, prednisolone, propranolol, and Lugol's iodine	Recovered within 10 weeks

M, male; F, female; ALT, alanine aminotransferase; ALP, alkaline phosphatase; GGT, gamma glutamyl transpeptidase; TBil, total bilirubin; TSH, thyroid-stimulating hormone.

Liver injury usually occurs within 2 days to 3 months after taking MMI.^{27,38} An older age of patients and a higher dose of MMI are associated with occurrence of

cholestasis.²⁷ However, in a recent study, cholestasis was found to be dose independent of MMI.²⁹ Therefore, MMI-induced cholestasis is idiopathic and unpredictable,

and autoimmune mechanisms may be involved in its occurrence.²⁹

Concomitant autoimmune liver diseases, including autoimmune hepatitis and primary biliary cirrhosis, as causes of cholestasis have only been reported in a few case reports describing hyperthyroidism in patients.^{7,8,39,40} This indicates that concomitant autoimmune liver diseases are not a common cause of cholestasis in these patients. However, other underlying liver diseases should also be excluded in patients with hyperthyroidism and cholestasis,

especially in high epidemic countries of hepatitis B or C virus. Kang et al. reported MMI-induced acute liver failure in a patient who was a chronic hepatitis B virus carrier.⁴¹

As shown in Table 3, patients in most previous case reports of MMI-associated severe cholestasis also had hyperthyroidism. Therefore, determining the causes of cholestasis in patients with MMI-treated hyperthyroidism is difficult, based solely on the clinical and biochemical presentation. A previous case report suggested that

Table 3. Previous case reports of methimazole-induced severe cholestasis.

Authors	Patients (M or F/years)	Laboratory data	Methimazole	Treatment	Outcome
Woeber KA, et al. ²⁷	F/36	TBil, 12.1 mg/dL ALT, 127 U/L ALP, 265 U/L TSH, <0.03 mIU/L	40 mg/day for 19 days	Methimazole was discontinued and radioactive iodine was used	Recovered within several weeks
Gallelli L, et al. ³⁷	M/54	TBil, 4.4 mg/dL ALT, 55 U/L ALP, 374 U/L TSH, 0.01 μ U/mL	30 mg/day for 5 months	Methimazole was discontinued and radioactive iodine was used	Recovered within 6 months
Yang J, et al. ³²	M/51	TBil, 385 μ mol/L ALT, 89 U/L TSH, 0.001 μ IU/mL	20 mg/day for 4 weeks	Methimazole was discontinued and radioactive iodine was used	Recovered within 5 weeks
Hung YT, et al. ³⁸	M/71	DBil, 680 μ mol/L ALT, 40 U/L ALP, 600 U/L TSH, normal	A 5-month course of methimazole	Cholestyramine, ursodeoxycholic acid, and chlorpheniramine	Recovered within 1 year
Ji H, et al. ⁴²	M/69	TBil, 370.3 μ mol/L ALT, 59.2 U/L ALP, 631 U/L TSH, 0.01 μ IU/mL	30 mg/day for 4 weeks	Methimazole was discontinued and radioactive iodine was used	Recovered within 2 weeks
Zou H, et al. ³	F/51 F/42	TBil, 105.8 μ mol/L ALT, 120 U/L ALP, 200 U/L TSH, <0.005 mIU/L TBil, 268.8 μ mol/L ALT, 135 U/L ALP, 353 U/L TSH, 0.008 mIU/L	30 mg/day for 8 days 30 mg/day for 2 weeks	Methimazole was discontinued and propylthiouracil was used Methimazole was discontinued; radioactive iodine and prednisolone were used	Recovered within 4 weeks Recovered within 16 weeks

M, male; F, female; ALT, alanine aminotransferase; ALP, alkaline phosphatase; TBil, total bilirubin; DBil, direct bilirubin; TSH, thyroid-stimulating hormone.

the RUCAM scale provided a more accurate measurement in determining the causality of MMI-induced hepatotoxicity than other methods.⁴² However, this scale needs to be verified in larger number of patients. Additionally, the RUCAM scale is based on ALP from hepatic origin only.⁴³ As stated above, bone isoenzymes of ALP are significantly increased in patients with hyperthyroidism, indicating that the RUCAM scale is also inaccurate in determining the causality of ATD-induced cholestasis. The RUCAM scale score for MMI was 7 in our patient, but his liver function worsened after MMI was discontinued. Therefore, we could not exclude thyrotoxicosis-induced cholestasis. TBil levels rapidly decreased after his hyperthyroidism resolved, which further supports the causality between thyrotoxicosis and cholestasis in our patient.

Treatment of cholestasis in patients with hyperthyroidism remains a significant challenge in clinical practice. For patients with suspected ATD-induced cholestasis, ATDs should be discontinued. For patients with thyrotoxicosis-induced cholestasis, rapid restoration of euthyroidism is important for the recovery of liver function.⁹

Previous studies have shown that control of hyperthyroidism is important for recovery of cholestasis, induced by MMI or hyperthyroidism.^{9,28} However, the choice of treatment methods for hyperthyroidism is complicated in clinical practice. Although there has been a report of successful switching to PTU after MMI-induced liver injury,³ it was not recommended because of cross-allergic reactions that might exist between PTU and MMI.⁴⁴ ATDs may aggravate liver injury and occasionally induce liver failure. Therefore, use of ATDs in patients with thyrotoxicosis-induced severe cholestasis is risky. Urgent thyroidectomy is also considered risky in patients with thyrotoxicity and severe liver dysfunction. Most previous studies have

shown that radioactive iodine therapy is a safe and effective treatment strategy in patients with MMI- or thyrotoxicosis-induced cholestasis,^{32,45} although radioactive iodine therapy has also been reported to cause hepatic injury on occasion.^{46,47}

Glucocorticoids have been successfully used for treating cholestatic hepatitis caused by MMI and thyrotoxicosis.⁴⁸ Glucocorticoids reduce conversion of thyroxine to triiodothyronine in peripheral tissues and decrease serum thyroxine levels in patients with hyperthyroidism by reducing thyroxine secretion.⁴⁹ Additionally, previous studies have shown that corticosteroids are effective in reducing peripheral oxidative stress present in infiltrative Graves' ophthalmopathy.^{50,51} In animal studies, other antioxidants, including vitamin E, curcumin, and L-carnitine, have been shown to alleviate L-thyroxine-induced oxidative stress in rat liver;^{52,53} however, their clinical efficacy remains to be demonstrated. An artificial liver support system has also been found to be effective in treating patients with ATD-induced cholestasis by decreasing thyroid hormone and bilirubin levels and promoting recovery of liver injury.⁵⁴

In conclusion, distinguishing between thyrotoxicosis- and MMI-induced severe cholestasis is difficult. Discontinuing MMI, treatment with glucocorticoids, and control of hyperthyroidism with radioactive iodine may be effective treatment methods for severe cholestasis induced by thyrotoxicosis or MMI in patients with hyperthyroidism.


Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Funding

This work was supported by the Funds of Chinese National Natural Science Foundation Project (81460124, 81860114).

ORCID iD

Shide Lin  <https://orcid.org/0000-0001-8803-4069>

References

1. Lin TY, Shekar AO, Li N, et al. Incidence of abnormal liver biochemical tests in hyperthyroidism. *Clin Endocrinol* 2017; 86: 755–759. doi: 10.1111/cen.13312.
2. Burra P. Liver abnormalities and endocrine diseases. *Best Pract Res Clin Gastroenterol* 2013; 27: 553–563. doi: 10.1016/j.bpg.2013.06.014.
3. Zou H, Jin L, Wang LR, et al. Methimazole-induced cholestatic hepatitis: two cases report and literature review. *Oncotarget* 2016; 7: 5088–5091. doi: 10.18632/oncotarget.6144.
4. Wickramasinghe RDSS, Luke WANV, Sebastianpillai BS, et al. Thyrotoxic crisis presenting with jaundice. *BMC Res Notes* 2016; 9: 320. doi: 10.1186/s13104-016-2126-z.
5. Regelman MO, Miloh T, Arnon R, et al. Graves' disease presenting with severe cholestasis. *Thyroid* 2012; 22: 437–439. doi: 10.1089/thy.2011.0267.
6. Elias RM, Dean DS and Barsness GW. Hepatic dysfunction in hospitalized patients with acute thyrotoxicosis: a decade of experience. *ISRN Endocrinol* 2012; 2012: 325092. doi: 10.5402/2012/325092.
7. Jhee JH, Kim HJ, Kang W, et al. A case of autoimmune hepatitis combined with Graves' disease. *Korean J Gastroenterol* 2015; 65: 48–51. doi: 10.4166/kjg.2015.65.1.48
8. Koyamada R, Higuchi T, Kitada A, et al. Association of primary biliary cirrhosis-autoimmune hepatitis overlap syndrome with immune thrombocytopenia and Graves' disease. *Intern Med* 2015; 54: 2013–2016. doi: 10.2169/internalmedicine.54.4405.
9. Wang R, Tan J, Zhang G, et al. Risk factors of hepatic dysfunction in patients with Graves' hyperthyroidism and the efficacy of (131)iodine treatment. *Medicine* 2017; 96: e6035. doi: 10.1097/md.00000000000006035.
10. Tibi L, Patrick AW, Leslie P, et al. Alkaline phosphatase isoenzymes in plasma in hyperthyroidism. *Clin Chem* 1989; 35: 1427–1430. doi: 10.1080/03079459608419185
11. Gurlek A, Cobankara V and Bayraktar M. Liver tests in hyperthyroidism: effect of antithyroid therapy. *J Clin Gastroenterol* 1997; 24: 180–183. doi: 10.1097/00004836-199704000-00013
12. Azizi F. Gamma-glutamyl transpeptidase levels in thyroid disease. *Arch Intern Med* 1982; 142: 79–81. doi: 10.1001/archinte.142.1.79
13. Viallard JF, Tabarin A, Neau D, et al. Hyperthyroidism with severe intrahepatic cholestasis. *Dig Dis Sci* 1999; 44: 2001–2002. doi: 10.1023/a: 1026662032737
14. Majeed M and Babu A. Cholestasis secondary to hyperthyroidism made worse by methimazole. *Am J Med Sci* 2006; 332: 51–53. doi: 10.1097/00000441-200607000-00012
15. Hull K, Horenstein R, Naglieri R, et al. Two cases of thyroid storm-associated cholestatic jaundice. *Endocr Pract* 2007; 13: 476–480. doi: 10.4158/ep.13.5.476.
16. Soysal D, Tatar E, Solmaz S, et al. A case of severe cholestatic jaundice associated with Graves' disease. *Turk J Gastroenterol* 2008; 19: 77–79.
17. Ichikawa H, Ebinuma H, Tada S, et al. A case of severe cholestatic jaundice with hyperthyroidism successfully treated with methimazole. *Clin J Gastroenterol* 2009; 2: 315–319. doi: 10.1007/s12328-009-0094-8.
18. Kibirige D, Kiggundu DS, Sanya R, et al. Cholestatic hepatic injury due to a thyroid storm: a case report from a resource limited setting. *Thyroid Res* 2012; 5: 6. doi: 10.1186/1756-6614-5-6.
19. Yan LD, Thomas D, Schwartz M, et al. Rescue of Graves thyrotoxicosis-induced cholestatic liver disease without antithyroid drugs: a case report. *J Endocr Soc* 2017; 1: 231–236. doi: 10.1210/js.2016-1065.
20. Fong TL, McHutchison JG and Reynolds TB. Hyperthyroidism and hepatic dysfunction. A case series analysis. *J Clin Gastroenterol* 1992; 14: 240–244. doi: 10.1097/00004836-199204000-00010
21. Soylyu A, Taskale MG, Ciltas A, et al. Intrahepatic cholestasis in subclinical and overt hyperthyroidism: two case reports.

- J Med Case Rep* 2008; 2: 116. doi: 10.1186/1752-1947-2-116.
22. Grattagliano L, Bonfrate L, Diogo C, et al. Biochemical mechanisms in drug-induced liver injury: certainties and doubts. *World J Gastroenterol* 2009; 15: 4865–4876. doi: 10.3748/wjg.15.4865.
 23. Heidari R, Niknahad H, Jamshidzadeh A, et al. An overview on the proposed mechanisms of antithyroid drugs-induced liver injury. *Adv Pharm Bull* 2015; 5: 1–11. doi: 10.5681/apb.2015.001.
 24. Myers JD, Brannon ES and Holland BC. A correlative study of the cardiac output and the hepatic circulation in hyperthyroidism. *J Clin Invest* 1950; 29: 1069–1077. doi: 10.1172/jci102338.
 25. Upadhyay G, Singh R, Kumar A, et al. Severe hyperthyroidism induces mitochondria-mediated apoptosis in rat liver. *Hepatology* 2004; 39: 1120–1130. doi: 10.1002/hep.20085
 26. Das K and Chainy GB. Modulation of rat liver mitochondrial antioxidant defence system by thyroid hormone. *Biochim Biophys Acta* 2001; 1537: 1–13. doi: 10.1016/S0925-4439(01)00048-5
 27. Woeber KA. Methimazole-induced hepatotoxicity. *Endocr Pract* 2002; 8: 222–224. doi: 10.4158/ep.8.3.222.
 28. Cooper DS: Antithyroid drugs. *N Engl J Med* 2005; 352: 905–917. doi: 10.1056/NEJMra042972.
 29. Wang MT, Lee WJ, Huang TY, et al. Antithyroid drug-related hepatotoxicity in hyperthyroidism patients: a population-based cohort study. *Br J Clin Pharmacol* 2014; 78: 619–629. doi: 10.1111/bcp.12336.
 30. Casallo Blanco S, Valero MA, Marcos Sanchez F, et al. Methimazole and propylthiouracil induced acute toxic hepatitis. *Gastroenterol Hepatol* 2007; 30: 268–270.
 31. Niculescu DA, Dusceac R, Galoiu SA, et al. Serial changes of liver function tests before and during methimazole treatment in thyrotoxic patients. *Endocr Pract* 2016; 22: 974–979. doi: 10.4158/EP161222.OR.
 32. Yang J, Li LF, Xu Q, et al. Analysis of 90 cases of antithyroid drug-induced severe hepatotoxicity over 13 years in china. *Thyroid* 2015; 25: 278–283. doi: 10.1089/thy.2014.0350.
 33. Papachristos DA, Huynh J, Grossman M, et al. Liver dysfunction and anti-thyroid therapy. *SAGE Open Med Case Rep* 2015; 3: 2050313X14568335. doi: 10.1177/2050313x14568335.
 34. Chou C, Wong RJ, Higgins JP, et al. Acute liver failure: a potential complication of antithyroid medication use. *Dig Dis Sci* 2015; 60: 1924–1927. doi: 10.1007/s10620-014-3389-7.
 35. Kulaksizoglu M, Gonen MS, Kebapcilar L, et al. Multiorgan dysfunction accompanied with metimazole and thyroid storm. *Transfus Apher Sci* 2012; 46: 149–152. doi: 10.1016/j.transci.2012.01.001.
 36. Shen C, Zhao CY, Liu F, et al. Acute-on-chronic liver failure due to thiamazole in a patient with hyperthyroidism and trilogy of fallot: case report. *BMC Gastroenterol* 2010; 10: 93. doi: 10.1186/1471-230x-10-93.
 37. Gallelli L, Staltari O, Palleria C, et al. Hepatotoxicity induced by methimazole in a previously health patient. *Curr Drug Saf* 2009; 4: 204–206. doi: 10.2174/157488609789006912.
 38. Hung YT, Yu WK and Chow E. Delayed cholestatic hepatitis due to methimazole. *Hong Kong Med J* 1999; 5: 200–201.
 39. Yasar DG, Ozenirler S and Dogan M. A patient with primary biliary cirrhosis accompanied by Graves disease and Hurthle cell adenoma. *Turk J Gastroenterol* 2007; 18: 198–200.
 40. Suzuki Y, Ishida K, Takahashi H, et al. Primary biliary cirrhosis associated with Graves' disease in a male patient. *Clin J Gastroenterol* 2016; 9: 99–103. doi: 10.1007/s12328-016-0635-x.
 41. Kang H, Choi JD, Jung IG, et al. A case of methimazole-induced acute hepatic failure in a patient with chronic hepatitis B carrier. *Korean J Intern Med* 1990; 5: 69–73. doi: 10.3904/kjim.1990.5.1.69
 42. Ji H, Yue F, Song J, et al. A rare case of methimazole-induced cholestatic jaundice in an elderly man of Asian ethnicity with hyperthyroidism: a case report. *Medicine* 2017; 96: e9093. doi: 10.1097/md.00000000000009093.

43. Danan G and Teschke R. Rucam in drug and herb induced liver injury: the update. *Int J Mol Sci* 2016; 17: 14. doi: 10.3390/ijms17010014.
44. Sadoul JL, Canivet B and Freychet P. Toxic hepatitis induced by antithyroid drugs: four cases including one with cross-reactivity between carbimazole and benzylthiouracil. *Eur J Med* 1993; 2: 473–477.
45. Ding Y, Xing J, Qiu Z, et al. Radioactive iodine therapy without recent antithyroid drug pretreatment for hyperthyroidism complicated by severe hyperbilirubinemia due to hepatic dysfunction: experience of a Chinese medical center. *Endocr Pract* 2016; 22: 173–179. doi: 10.4158/ep15736.or.
46. Hasan MK, Tierney WM and Baker MZ. Severe cholestatic jaundice in hyperthyroidism after treatment with 131-iodine. *Am J Med Sci* 2004; 328: 348–350. doi: 10.1016/S0002-9629(15)33945-8.
47. Kim CW, Park JS, Oh SH, et al. Drug-induced liver injury caused by iodine-131. *Clin Mol Hepatol* 2016; 22: 272–275. doi: 10.3350/cmh.2015.0037.
48. Zhang M, Zhou H, He R, et al. Steroids for the treatment of methimazole-induced severe cholestatic jaundice in a 74-year-old woman with type 2 diabetes. *Endocrine* 2010; 37: 241–243. doi: 10.1007/s12020-009-9305-9.
49. Panzer C, Beazley R and Braverman L. Rapid preoperative preparation for severe hyperthyroid Graves' disease. *J Clin Endocrinol Metab* 2004; 89: 2142–2144. doi: 10.1210/jc.2003-031981.
50. Bednarek J, Wysocki H and Sowinski J. Peripheral parameters of oxidative stress in patients with infiltrative Graves' ophthalmopathy treated with corticosteroids. *Immunol Lett* 2004; 93: 227–232. doi: 10.1016/j.imlet.2004.03.020.
51. Akarsu E, Buyukhatipoglu H, Aktaran S, et al. Effects of pulse methylprednisolone and oral methylprednisolone treatments on serum levels of oxidative stress markers in Graves' ophthalmopathy. *Clin Endocrinol* 2011; 74: 118–124. doi: 10.1111/j.1365-2265.2010.03904.x.
52. Yildirim S, Yildirim A, Dane S, et al. Dose-dependent protective effect of l-carnitine on oxidative stress in the livers of hyperthyroid rats. *Eurasian J Med* 2013; 45: 1–6. doi: 10.5152/eajm.2013.01.
53. Subudhi U and Chainy GB. Expression of hepatic antioxidant genes in l-thyroxine-induced hyperthyroid rats: regulation by vitamin e and curcumin. *Chem Biol Interact* 2010; 183: 304–316. doi: 10.1016/j.cbi.2009.11.004.
54. Wu DB, Chen EQ, Bai L, et al. Propylthiouracil-induced liver failure and artificial liver support systems: a case report and review of the literature. *Ther Clin Risk Manag* 2017; 13: 65–68. doi: 10.2147/tcrm.s122611.