Print ISSN: 2321-6379
Online ISSN: 2321-595X
DOI: 10.17354/ijss/2016/469

Case Report

Carbimazole-induced Cholestatic Hepatitis in Toxic Multinodular Goiter

R Amith, H M Madhukara

Consultant Physician, Gandhi Hospital, Kamareddy, Nizamabad, Telangana, India

Abstract

Antithyroid drugs are the treatment option for toxic multinodular goiter. Carbimazole is usually the drug of choice except in pregnancy where propylthiouracil is used. It is well tolerated and common side effects include allergy, upper GI upset, and rarely agranulocytosis. Hepatitis is another rare but serious complication. Hereby, we report a case of 55 years female with toxic nodular goiter, who developed cholestatic hepatitis after carbimazole therapy for 2 months. She recovered completely following withdrawal of the drug.

Key words: Carbimazole, Cholestatic hepatitis, Toxic multinodular jaundice

INTRODUCTION

Toxic multinodular goiter (Plummer's disease) is the 2nd most common cause for hyperthyroidism after Grave's disease. It accounts for 15-30% cases. Toxic nodular goiter (TNG) is more common in elderly (>50 years) and in women. Unlike Grave's disease which is autoimmune and antithyroid are started universally, TNG is not known to recur after therapy. Hence, surgery or radioiodine is the treatment of choice. Antithyroid is still used for symptomatic relief in patients waiting for surgery. It has several side effects the majority are mild and include allergic reactions and upper GI intolerance. Other side effects include agranulocytosis and vasculitis-like reaction particularly with propylthiouracil (PTU). Hepatotoxicity is rare, but serious side effects with both carbimazole and PTU. Fatal cases have been documented with both drugs.[4] The hepatic histology with PTU is toxic hepatitis and necrosis and it is cholestatic hepatitis with carbimazole. We present a case of carbimazole-induced cholestatic hepatitis in a patient with TNG. Clinical and biochemical findings in this patient with relevant review of literature are presented.

Access this article online

www.ijss-sn.com

Month of Submission : 06-2016
Month of Peer Review : 07-2016
Month of Acceptance : 08-2016
Month of Publishing : 08-2016

CASE REPORT

A 55-year-old female patient presented to the surgical outpatient department with chief complaints of progressive swelling over the neck for the last 10 years which has become symptomatic in the form of difficulty in swallowing for the last 4 months. She also has associated complaints of palpitations, weight loss of 5 kg and bilateral bulging eyes. There were no associated comorbidities. No h/o liver disease. She had no history of any addiction. On examination, her weight was 50 kg. She had a pulse rate of 112/min, regular; B.P was 140/85 mmHg. Ophthalmic examination showed bilateral exophthalmos. Systemic examination was normal. Thyroid swelling measured 8 x 6 cm, which was firm nontender with nodular surface and no bruit, was heard.

Her initial T4 was 23.1 μg/dl, T3-2.56 ng/dl and thyroid stimulating hormone <0.01. She was diagnosed as a case of toxic multinodular goiter and discharged on tablet propranolol 40 mg daily and carbimazole 40 mg/day. I^{131} was not started as fear of exacerbating eye manifestations was there. However, she re-presented 4 weeks later with progressively deepening jaundice, pruritus, and passage of clay-colored stools. There was no previous history of jaundice, blood transfusions, intravenous drug abuse, anesthesia, recent history of travel, or animal exposure. She was markedly jaundiced on examination. There were no peripheral stigmata of chronic liver disease. There was no right hypochondrial tenderness, hepatomegaly, features of

Corresponding Author: Dr. H M Madhukara, Consultant Physician, Gandhi Hospital, Kamareddy, Nizamabad, Telangana, India.
E-mail: makhm564@gmail.com

hepatic encephalopathy, or cardiac decompensation. Results of the liver function tests are shown in the table. The lab findings were suggestive of cholestatic jaundice. Her serology was negative for hepatitis A anti-IgM antibody, hepatitis B surface antigen, hepatitis B core anti-IgM, hepatitis B surface anti-IgM, hepatitis B antigen, and hepatitis C virus anti-IgM. Her ANA, AMA, and anti-LKM antibodies were negative. The abdominal ultrasound demonstrated a normal sized liver with no focal lesions. The bile ducts, pancreas, kidney, and spleen were all reported as normal. Contrast-enhanced computed tomography abdomen and magnetic resonance cholangiopancreatography did not reveal any obstruction in the biliary tract. A liver biopsy was undertaken once contraindications to the procedure (such as derangements in coagulation profile) had been excluded which showed intrahepatic cholestasis. Carbimazole was stopped suspecting a drug-induced pathology and follow-up Liver function tests (LFTs) were done.

The patient is was put on propranolol and prednisolone in the interim for her thyrotoxicosis and exophthalmoses. Her liver function tests improved significantly following stoppage of carbimazole. The high degree of alkaline phosphatase could also be due to the effect of hyperthyroidism on bone resorption. She is currently euthyroid (Figures 1-4 and Table 1).

Figure 1: Female patient with goiter and jaundice

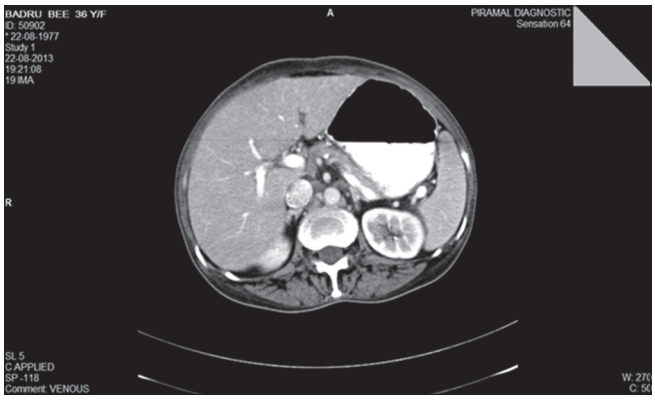

Figure 2: Contrast-enhanced computed tomography abdomen showing no abnormality in liver or biliary tracts

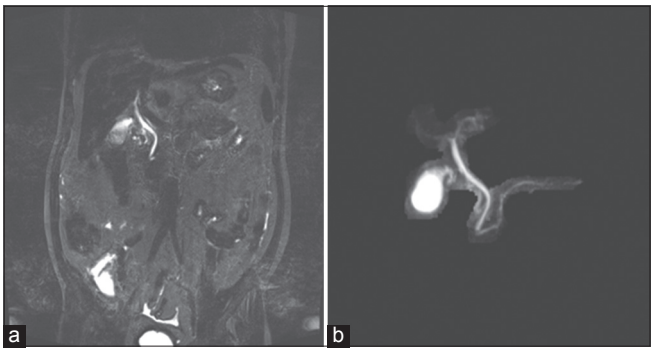

Figure 3: (a and b) Magnetic resonance cholangiopancreatography showing no obstruction to the biliary tract hence ruling out any obstruction as a cause of jaundice

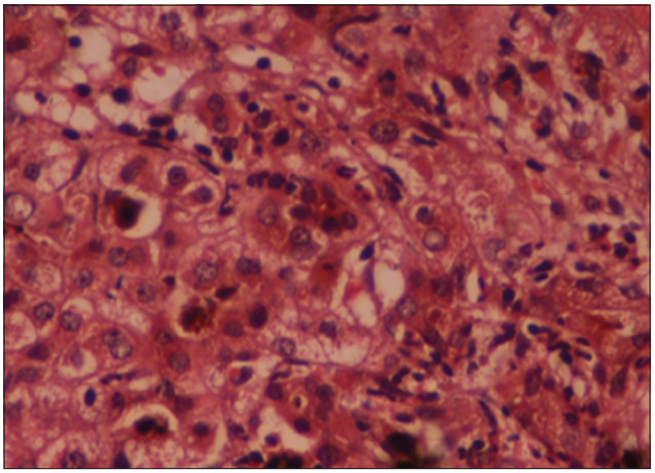

Figure 4: Biopsy specimen showing intrahepatic cholestatsis

Table 1: Serial LFT reports showing her course of illness

LFTS	Normal	20/7/2015	24/7/2015	1/8/2015	14/8/2015	28/8/2015
Serum bilirubin total (mg/dl)	0.3-1.3	27.6	25.4	20.6	11.6	4.5
Serum bilirubin direct (mg/dl)	0.1-0.4	17.4	16.8	14.38	7.54	2.1
SGOT (U/L)	12-38	165	112	96	65	45
SGPT (U/L)	7-41	112	100	88	59	44
Serum protein (U/L)	7-9	5.3	6.4	6.3	6.4	6.6
Serum albumin (U/L)	4-6	3.3	3.8	3.3	3.6	3.8
Alk phosphatase (U/L)	4-126	2300	2215	1732	1164	668

SGOT: Serum glutamic oxaloacetic transaminase, SGPT: Serum glutamate-pyruvate transaminase, LFT: Liver function tests

DISCUSSION

Thyroid dysfunction may perturb liver function, and the liver modulates thyroid hormone metabolism. A variety of systemic diseases and drugs may affect both organs.[1,2]

Thyrotoxicosis and Hepatobiliary Injury

Abnormal liver biochemical test results have been reported in hyperthyroid patients before and after antithyroid therapy. Gurlek *et al*.[3] showed that 60.5% of 43 patients with hyperthyroidism had at least one liver abnormality at diagnosis. Hepatic damage occurring from thyrotoxicosis per se has been ascribed to ischemic injury resulting from a relative decrease in blood flow despite increased metabolic activity of the liver.[1] But bear in mind that raised alkaline phosphatase may not be of liver origin but rather from bone, indicating an osteoblastic response to thyroid hormone-induced bone resorption.

The nature of hepatic injury caused by thionamides is dependent on the specific drug. While carbimazole and its active metabolite methimazole typically cause cholestasis, PTU is notable for causing hepatocellular injury.[4-7] Thionamide-induced liver damage is an idiosyncratic reaction that can develop at any time, but usually occurs within the first 3 months of treatment. It occurs in about 1% of patients with a predisposition for women younger than 30 years of age.[1] The mechanism of injury is thought to be based on an allergic host response.[1,4,8]

Our patient had a predominantly cholestatic hepatitis, which is consistent with cases of carbimazole- and methimazole-induced hepatic damage reported in the literature.[9-11] Thionamide therapy may be an additional insult to the liver. Ai-Leng *et al*.[12] reported a case of fatal hepatic failure in a patient on carbimazole and bupropion, while Enghofer *et al*.[13] reported fulminant hepatitis A infection in a hyperthyroid patient treated with carbimazole. Therefore, we suggest that it might be prudent to exclude additional risk factors for the liver injury in patients presenting with thionamide-associated cholestasis.

Our patient developed significant hyperbilirubinemia within 4 weeks of starting therapy with significant elevation of alkaline phosphatase. The aminotransferases were mildly elevated, reaching two-three times the normal. She showed good response to withdrawal of drug and is currently doing well. Cholestatic hepatitis developing due to carbimazole in TNG has not been described in the past and has only been described in patients with Grave's disease.[14-15]

CONCLUSION

- Jaundice as a complication of thionamide treatment of hyperthyroidism is rare.
- This complication cannot be predicted by deranged liver enzymes at presentation, but typically occurs within 3 months of therapy.
- It can be fatal, particularly when there are additional hepatotoxic factors.
- The drug must be withdrawn immediately and alternative therapy for hyperthyroidism, such as radioiodine must be considered in appropriate patients.

REFERENCES

1. Malik R, Hodgson H. The relationship between the thyroid gland and the liver. QJM 2002;95:559-69.
2. Borzio M, Caldara R, Borzio F, Piepoli V, Rampini P, Ferrari C. Thyroid function tests in chronic liver disease: Evidence for multiple abnormalities despite clinical euthyroidism. Gut 1983;24:631-6.
3. Gürlek A, Cobankara V, Bayraktar M. Liver tests in hyperthyroidism: Effect of antithyroid therapy. J Clin Gastroenterol 1997;24:180-3.
4. Cooper DS. Antithyroid drugs. N Engl J Med 2005;352:905-17.
5. Weetman AP. Graves' disease. N Engl J Med 2000;343:1236-48.
6. Ruiz JK, Rossi GV, Vallejos HA, Brenet RW, Lopez IB, Escribano AA. Fulminant hepatic failure associated with propylthiouracil. Ann Pharmacother 2003;37:224-8.
7. Liaw YF, Huang MJ, Fan KD, Li KL, Wu SS, Chen TJ. Hepatic injury during propylthiouracil therapy in patients with hyperthyroidism. A cohort study. Ann Intern Med 1993;118:424-8.
8. Williams KV, Nayak S, Becker D, Reyes J, Burmeister LA. Fifty years of experience with propylthiouracil-associated hepatotoxicity: What have we learned? J Clin Endocrinol Metab 1997;82:1727-33.
9. Arab DM, Malatjalian DA, Rittmaster RS. Severe cholestatic jaundice in uncomplicated hyperthyroidism treated with methimazole. J Clin Endocrinol Metab 1995;80:1083-5.
10. Blom H, Stolk J, Schreuder HB, von Blomberg-van der Flier M. A case of carbimazole-induced intrahepatic cholestasis. An immune-mediated reaction? Arch Intern Med 1985;145:1513-5.
11. Schwab GP, Wetscher GJ, Vogl W, Redmond E. Methimazole-induced cholestatic liver injury mimicking sclerosing cholangitis. Langenbecks Arch Surg 1996;381:225-7.
12. Khoo AL, Tham LS, Lee KH, Lim GK. Acute liver failure with concurrent bupropion and carbimazole therapy. Ann Pharmacother 2003;37:220-3.
13. Enghofer M, Badenhoop K, Zeuzem S, Schmidt-Matthiesen A, Betz C, Encke A, *et al.* Fulminant hepatitis A in a patient with severe hyperthyroidism: Rapid recovery from hepatic coma after plasmapheresis and total thyroidectomy. J Clin Endocrinol Metab 2000;85:1765-9.
14. Waseem M, Seshadri KG, Kabadi UM. Successful outcome with methimazole and lithium combination therapy for propylthiouracil-induced hepatotoxicity. Endocr Pract 1998;4:197-200.
15. Kota SK, Meher LK, Kota SK, Jammula S, Modi KD. Carbimazole-induced cholestatic hepatitis in Graves' disease. Indian J Endocrinol Metab 2013;17:326-8.

How to cite this article: Amith R, Madhukara HM. Carbimazole-induced Cholestatic Hepatitis in Toxic Multinodular Goiter. Int J Sci Stud 2016;4(5):252-254.

Source of Support: Nil, **Conflict of Interest:** None declared.