

Internal Medicine
Section

Cholestatic Liver Injury following Re-initiation of Carbimazole in a Patient with Graves' Disease: A Case Report

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ABSTRACT

Carbimazole is a commonly used Antithyroid Drug (ATD) for the treatment of Graves' Disease (GD). Although generally well tolerated, it can rarely cause drug-induced liver injury, typically presenting with a cholestatic pattern. Carbimazole-induced cholestatic liver injury is an uncommon and often underrecognised complication that may pose a diagnostic challenge. In this case, a 46-year-old man presented with jaundice for one month, along with pruritus, nausea, anorexia, weight loss, palpitations, heat intolerance, and tremors. He had GD and had been off treatment for nearly one year before restarting carbimazole 10 mg twice daily two months before presentation. The patients had symptoms of hyperthyroidism and jaundice. Laboratory tests showed conjugated hyperbilirubinaemia with a cholestatic pattern of liver injury and preserved liver synthetic function. Thyroid function tests confirmed thyrotoxicosis, and positive thyroid autoantibodies were consistent with GD as the underlying aetiology. Viral markers and autoimmune liver tests were negative. Imaging ruled out biliary obstruction, and liver biopsy showed cholestatic injury with canalicular bile plugs, consistent with carbimazole-induced cholestatic liver injury. Carbimazole was stopped, and two cycles of low-volume plasma exchange were performed. Thyrotoxicosis was controlled with Lugol's iodine, dexamethasone, and propranolol, followed by total thyroidectomy. This case highlights that even late presentation and toxicity following re-initiation of carbimazole should be considered in patients presenting with cholestatic liver injury.

Keywords: Hyperbilirubinaemia, Jaundice, Plasma exchange, Thyroidectomy, Thyrotoxicosis

CASE REPORT

A 46-year-old man presented with progressively worsening jaundice for one month, associated with pruritus, nausea, anorexia, and significant weight loss. He also reported palpitations, heat intolerance, and tremors. He had been diagnosed with GD approximately three years earlier and was initially treated with carbimazole 10 mg twice daily for approximately two years. After achieving a euthyroid state, carbimazole was discontinued, and he remained off treatment for nearly one year. Following recurrence of symptoms of thyrotoxicosis, carbimazole was restarted at a dose of 10 mg twice daily, two months before presentation. Approximately, one month after re-initiation of carbimazole, he developed jaundice, which progressively worsened over the following month despite continued treatment. There was no history of alcohol use, non-steroidal anti-inflammatory drug intake, herbal medication use, blood transfusion, or risk factors for viral hepatitis.

On examination, the patient was alert and icteric. He had tachycardia and diffuse thyromegaly measuring 10 × 9 cm, with mild proptosis. The liver was palpable 2 cm below the costal margin. There was no splenomegaly or ascites. There were no stigmata or clinical signs of chronic liver disease.

Laboratory investigation revealed that total bilirubin was highly elevated at 30.4 mg/dL and direct bilirubin was also elevated at 19.6 mg/dL, indicating conjugated hyperbilirubinaemia. Aspartate Aminotransferase (AST) was 40 U/L and Alanine Aminotransferase (ALT) was 42 U/L. The R factor was calculated according to the updated Roussel Uclaf Causality Assessment Method (RUCAM). Using the laboratory values at presentation, the R factor was $(42/56) \div (532/147) = 0.21$, consistent with a cholestatic pattern of liver injury. Alkaline Phosphatase (ALP) was elevated at 532 U/L, indicating a cholestatic pattern of liver injury. Total protein was low at 4.7 g/dL, while albumin was 4.1 g/dL and International Normalised Ratio (INR) was 0.9, both within normal range, indicating intact liver synthetic function. Thyroid profile showed that Thyroid Stimulating

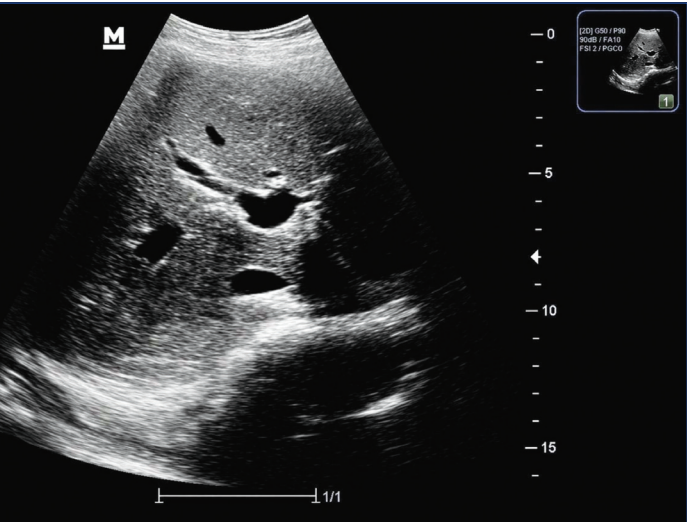
Hormone (TSH) was decreased at 0.001, while Free Triiodothyronine (FT3) was elevated at 15.6 and Free Thyroxine (FT4) was elevated at 5.2, indicating thyrotoxicosis. Anti thyroid peroxidase antibody (Anti-TPO) was elevated at a value greater than 1000 IU/mL, anti-Thyroglobulin Antibody (Anti-Tg) was elevated at 316 IU/mL, and TSH Receptor Antibody (TRAb) was elevated at 25.3 IU/L, which were consistent with GD as the underlying aetiology. Hepatitis B Surface Antigen (HBsAg), anti-Hepatitis C Virus antibody (Anti-HCV), Immunoglobulin M Epstein Barr virus (IgM EBV), Cytomegalovirus (CMV), total IgG, Anti-Smooth Muscle Antibody (ASMA), anti-Liver Kidney Microsomal type 1 antibody (Anti-LKM1), and Anti-Mitochondrial Antibody (AMA) were negative, which ruled out viral hepatitis, autoimmune liver diseases and primary biliary cholangitis [Table/Fig-1].

Parameter	Value	Reference range
Total bilirubin (mg/dL)	30.4	0.3-1.2
Direct bilirubin (mg/dL)	19.6	0.0-0.3
Aspartate aminotransferase (AST) (U/L)	40	10-40
Alanine aminotransferase (ALT) (U/L)	42	7-56
Alkaline phosphatase (ALP) (U/L)	532	44-147
Total protein (g/dL)	4.7	6.0-8.3
Albumin (g/dL)	4.1	3.5-5.0
International normalised ratio (INR)	0.9	0.8-1.2
Thyroid stimulating hormone (TSH) (μIU/mL)	0.001	0.4-4.0
Free triiodothyronine (FT3) (pg/mL)	15.6	2.3-4.2
Free thyroxine (FT4) (ng/dL)	5.2	0.8-1.8
Anti thyroid peroxidase antibody (Anti-TPO) (IU/mL)	greater than 1000	less than 35
Anti thyroglobulin antibody (Anti-Tg) (IU/mL)	316	less than 40
Thyroid stimulating hormone receptor antibody (TRAb) (IU/L)	25.3	less than 1.75

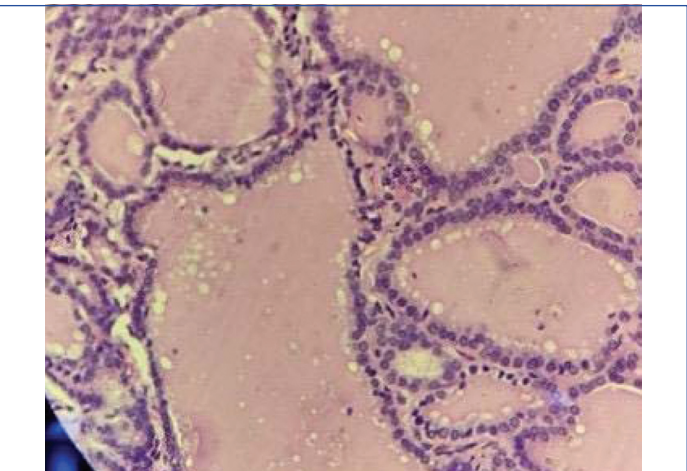
Hepatitis B surface antigen (HBsAg)	Negative	Negative
Anti hepatitis C virus antibody (Anti-HCV)	Negative	Negative
Immunoglobulin M Epstein Barr virus (IgM EBV)	Negative	Negative
Cytomegalovirus (CMV)	Negative	Negative
Total immunoglobulin G (IgG)	Negative	Normal
Anti smooth muscle antibody (ASMA)	Negative	Negative
Anti liver kidney microsomal type 1 antibody (Anti-LKM1)	Negative	Negative
Anti mitochondrial antibody (AMA)	Negative	Negative

[Table/Fig-1]: Baseline laboratory work-up.

Ultrasound abdomen showed grade 1 fatty liver without features of chronic liver disease, and portal vein Dopplers showed normal hepatopetal flow [Table/Fig-2]. Magnetic Resonance Cholangiopancreatography (MRCP) and Magnetic Resonance Imaging (MRI) abdomen excluded biliary obstruction. Following exclusion of biliary obstruction, viral hepatitis, and autoimmune liver disease, liver biopsy was subsequently performed to further evaluate the persistent cholestatic liver injury. Histopathological examination showed cholestatic injury with canalicular bile plugs and minimal inflammation, consistent with drug-induced liver injury (DILI) [Table/Fig-3]. Considering the temporal association with carbimazole re-initiation, exclusion of other common causes of liver injury, and a RUCAM score of 8, carbimazole was considered the most likely causative agent.

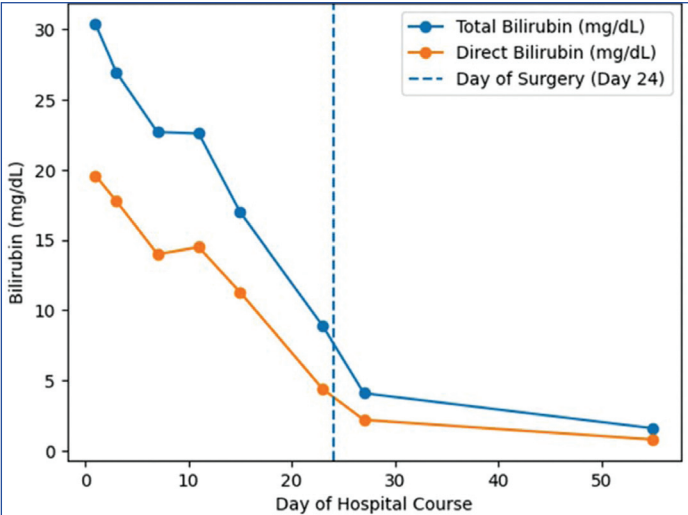


[Table/Fig-2]: Ultrasonographic image of the liver showing grade 1 fatty liver without features of chronic liver disease.



[Table/Fig-3]: Liver biopsy showing cholestatic injury with canalicular bile plugs and minimal inflammation (hematoxylin and eosin stain, X200 magnification).

Carbimazole was discontinued. Due to high bilirubin levels and risk of acute liver failure, the patient underwent two cycles of low-volume plasma exchange, which led to improvement in symptoms and reduction in serum bilirubin levels [Table/Fig-4]. As ATD were



[Table/Fig-4]: Changes in total and direct bilirubin levels during hospital stay, with day of surgery indicated.

contraindicated, thyrotoxicosis was controlled using Lugol's iodine (5-7 drops three times daily), dexamethasone (2 mg every 6 hours), and propranolol (40 mg three times daily). Once thyroid hormone levels became normal (euthyroid state), definitive management with total thyroidectomy was performed on day 24, as ATD could not be continued due to drug-induced liver injury. Serial laboratory parameters during hospital stay are shown in [Table/Fig-5].

Postoperatively, he was started on levothyroxine 75 µg once daily for thyroid hormone replacement. At one-month postoperative follow-up, liver function tests had normalised. He was continued on levothyroxine, initially at 50 µg once daily, with serial dose titration based on TSH levels, and remained on regular follow-up.

DISCUSSION

The GD is an autoimmune disorder that primarily affects the thyroid gland and is the most common cause of hyperthyroidism. GD is caused by thyroid-stimulating immunoglobulin (TSI), also known as thyroid-stimulating antibody (TSAb). TSI binds to the Thyroid-Stimulating Hormone (TSH) receptor on the thyroid cell membrane and mimics the action of TSH. It stimulates both thyroid hormone production and thyroid gland growth, resulting in hyperthyroidism and thyromegaly [1].

The three main treatment options for patients with Graves' hyperthyroidism are ATD, radioactive iodine, and surgery [2]. ATDs are generally the first-line treatment for patients with GD. Among the ATDs, carbimazole or methimazole is the most commonly used medication for inducing and maintaining remission in thyrotoxicosis, particularly in GD. Propylthiouracil (PTU) has limited indications because of its higher risk of hepatotoxicity [3]. Definitive treatment of GD is achieved through Radioactive Iodine Ablation (RAIA) or surgery. Surgery or RAIA may be considered in patients who fail to respond to ATDs or have contraindications to their use [4].

Carbimazole-induced cholestatic drug-induced liver injury is a rare but recognised adverse effect. Transient asymptomatic elevation of aminotransferases occurs in up to 30% of patients receiving ATD, whereas clinically significant drug-induced liver injury remains rare, accounting for only 0.03-0.5% of cases. The mechanisms underlying carbimazole-induced liver injury are not completely understood, but it is thought to involve an immuno-allergic response, potentially aggravated by the drug's metabolic pathways [5]. Histological examination of liver biopsies from affected patients often demonstrates portal tract oedema and inflammation, suggestive of a cholestatic process [6].

Carbimazole-induced liver injury is a serious idiosyncratic reaction that usually presents with cholestatic jaundice, most commonly within the first eight weeks of treatment [7]. In the present case, although

Parameter	Values								Reference
Day	1	3	7	11	15	23	27	55	—
Total bilirubin (mg/dL)	30.4	>27	22.7	22.6	>17	8.9	4.1	1.6	0.2-1.2
Direct Bilirubin (mg/dL)	19.6	17.8	14.0	14.5	11.3	4.4	2.2	0.8	0.0-0.3
Aspartate Aminotransferase (AST) (U/L)	40	45	51	53	51	42	44	44	10-40
Alanine Aminotransferase (ALT) (U/L)	42	44	56	54	55	48	47	54	7-56
Alkaline Phosphatase (ALP) (U/L)	532	505	417	432	480	422	167	124	44-147
Total protein (g/dL)	4.7	4.5	4.2	3.7	4.7	2.6	2.6	4.1	6.0-8.3
Albumin (g/dL)	4.1	3.8	3.9	3.5	3.7	3.3	3.6	3.5	3.5-5
INR	0.9	1.04	—	0.85	—	1.37	—	—	0.8-1.2
TSH (μIU/mL)	0.001	—	0.005	—	0.01	0.01	—	—	0.4-4
FT4 (ng/dL)	5.2	—	2.4	—	3.13	1.38	—	—	0.8-1.8
FT3 (pg/mL)	15.6	—	3.2	—	—	3.6	—	—	2.3-4.2

[Table/Fig-5]: Serial laboratory parameters during hospital stay.

"—" Not measured.

the patient had a previous history of carbimazole use, liver injury developed following re-initiation of therapy, suggesting an idiosyncratic reaction upon re-exposure rather than cumulative toxicity, which has rarely been reported. This case highlights that carbimazole toxicity should be considered even in delayed presentations of cholestatic liver injury. It also emphasises that liver injury may occur following re-initiation of treatment. The biochemical pattern of liver injury can be characterised using the R factor, calculated as (ALT/ALT ULN) ÷ (ALP/ALP ULN), as described in the updated RUCAM [8]. An R factor of 0.21 is consistent with a cholestatic pattern of liver injury. The RUCAM score was 8, indicating a probable causal relationship between carbimazole and liver injury.

Although the cholestatic parameters showed progressive improvement, AST remained mildly elevated above the upper reference limit during follow-up, with values of 51 U/L on day 7, 53 U/L on day 11, 51 U/L on day 15, 42 U/L on day 23, and 44 U/L on day 27 and day 55. INR was 1.37 on day 23, which was mildly above the upper reference limit. Total protein was also low, with a value of 4.7 g/dL at baseline and 2.6 g/dL on days 23 and 27. These laboratory abnormalities were noted during the hospital course. Extensive investigations in these reports, including viral hepatitis screening, Human Immunodeficiency Virus (HIV) testing, and autoimmune markers such as ANA-antinuclear antibody; ANCA-antineutrophil cytoplasmic antibody; AMA-antimitochondrial antibody; SMA-smooth muscle antibody were negative, thereby excluding other common causes of liver dysfunction [9]. Similar clinical and laboratory findings were observed in the present case, supporting the diagnosis of drug-induced cholestatic liver injury. Haouach S et al., reported a 29-year-old woman with GD who developed severe predominantly cholestatic hepatotoxicity two weeks after starting carbimazole. The significant feature was the use of plasmapheresis as bridging therapy to definitive thyroidectomy, with marked improvement in liver function following carbimazole withdrawal [7]. Al Hariri B et al., described a 42-year-old man who developed severe cholestatic jaundice four weeks after starting carbimazole. Liver biopsy confirmed cholestatic injury after viral, autoimmune, and biliary causes were excluded, and bilirubin levels gradually improved following withdrawal of carbimazole [9].

Karunathilake P et al., reported a 43-year-old woman who developed severe carbimazole-induced cholestatic hepatitis while remaining thyrotoxic. The patient underwent three sessions of therapeutic plasma exchange, resulting in clinical and biochemical improvement and allowing subsequent total thyroidectomy, highlighting the role of plasma exchange as a bridge to definitive treatment [10]. Alnajjar LA et al., reported a 17-year-old girl who developed both severe neutropenia and hepatotoxicity during long-term carbimazole therapy following dose modification. The case demonstrates that carbimazole toxicity may involve multiple serious adverse effects and

may occur even after prolonged treatment rather than exclusively during the initial weeks of therapy [11]. Campos F et al., described a patient with GD whose liver dysfunction worsened following initiation of carbimazole and improved rapidly after its withdrawal. The report emphasised the diagnostic difficulty in distinguishing thyrotoxicosis-related liver dysfunction from ATD-induced liver injury, an important consideration when evaluating abnormal liver function tests in GD [12]. In contrast to these reports, the present case developed cholestatic liver injury following re-initiation of carbimazole after previous exposure and a drug-free period of nearly one year. The patient presented with severe hyperbilirubinaemia and persistent thyrotoxicosis, while further use of ATD was contraindicated because of drug-induced liver injury.

Prompt discontinuation of carbimazole remains the cornerstone of management. In severe cases, plasma exchange may be used as a supportive therapy by removing circulating bilirubin, bile acids, ammonia, and inflammatory mediators, thereby providing stabilisation until definitive thyroid surgery can be performed [13,14]. Beta-blockers (e.g., propranolol) or calcium channel blockers (e.g., verapamil) are used to control palpitations, tremors, and anxiety while awaiting definitive treatment. If surgery is planned, patients are usually administered beta-blockers or iodine preparations (e.g., Lugol's solution) to reduce thyroid activity and prevent complications such as thyroid storm [15].

In the present case, two cycles of low-volume plasma exchange were performed, resulting in a progressive reduction in serum bilirubin levels. Thyrotoxicosis was controlled using Lugol's iodine (5-7 drops three times daily), dexamethasone (2 mg every 6 hours), and propranolol (40 mg three times daily). Once thyroid hormone levels normalised and a euthyroid state was achieved, definitive management with total thyroidectomy was performed. This case highlights the occurrence of carbimazole-induced liver injury following re-exposure and the challenge of managing thyrotoxicosis when conventional ATD cannot be continued.

CONCLUSION(S)

Carbimazole-induced cholestatic liver injury is a rare but important adverse effect that can present with prolonged jaundice and a cholestatic pattern on laboratory evaluation. In patients with GD, liver dysfunction may be due to multiple causes, making diagnosis challenging. Careful clinical assessment, exclusion of viral and autoimmune causes, appropriate imaging, and liver biopsy when required are essential to establish the diagnosis. In the present case, despite prior long-term treatment with carbimazole, liver injury developed after re-initiation of therapy, suggesting an idiosyncratic reaction on re-exposure. This case highlights that even late presentation and toxicity following re-initiation of carbimazole should be considered in patients presenting with cholestatic liver injury.

Early recognition and prompt withdrawal of carbimazole are key steps in management to prevent progression to severe liver injury. Supportive measures, including plasma exchange in selected cases, can help reduce bilirubin levels and stabilise the patient. When ATD cannot be continued, alternative measures to control thyrotoxicosis followed by definitive management with surgery provide a safe and effective treatment approach.

Patient consent: Written informed consent was obtained from the patient for publication of this case report and any accompanying images. The patient was informed about the purpose of publication and was provided an opportunity to review the manuscript prior to submission

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