Methimazole induced cholestatic jaundice in a 30-year-old hyperthyroid female patient

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ABSTRACT

Hyperthyroidism is one of the most common endocrinological disorders especially in females. Treatment is either pharmacological, surgical or by radioactive iodine uptake (1). Antithyroid drugs (ATD) are considered as the first line treatment unless they are contraindicated, with a very few cases who reported side effects (2). We report a 30-year-old female with hyperthyroidism, she started treatment with Methimazole 20 mg daily, within one month she presented with acute cholestatic liver insult not otherwise attributed. Symptoms and laboratory findings were decreased on withdrawal, but not normalized. Her condition was controlled by beta blockers and subsequently Prednisolone.

CASE REPORT

A 30-year-old female, recently married, visited our outpatient clinic, complaining of yellow discoloration of sclera, dark urine and pale stool. She had a history of controlled thyrotoxicosis under Methimazole one month before. Her laboratory investigation showed Free Thyroxine level (1.76 ng/dl) reference range (0.2-8.00 ng/dl), Thyroid stimulating hormone (0.01 IU/ml) reference range (0.25-4.00 IU/ml). Elevated total bilirubin (8.9 mg/dl) (152.1 μmol/L), direct bilirubin (7.1 mg/dl) (121.4 μmol/L) serum AST (123 IU/l), serum ALT (68 IU/l), serum Albumin (3.4 gm/dl) and normal coagulation profile were found. Serum Alkaline phosphatase of 200 U/L and GGT of 102 U/L. Hepatitis serology and autoimmune markers are negative.

Her body weight of 69 kg and height of 175cm were noted. Heart rate was 120 beat/min, Blood pressure was 140/90 mmHg. Physical examination did not show anything except slight icteric tinged sclera, even the Thyroid was not palpable. Abdominal ultrasound showed normal liver span, even intra splanchnic bed increases, and hypoxia causes hepatic injury (11).

Organ oxygen consumption but not blood flow augments with the increase in the osteoblastic activity (10). Autopsies in patients with hyperthyroidism had at least one liver abnormality at diagnosis. A study conducted by Gurlek et al. (7) showed that 60.5% of 43 patients with hyperthyroidism had at least one liver abnormality at diagnosis. Hence, a baseline liver profile is essential upon diagnosis of thyrotoxicosis. Routine testing of liver function during therapy with antithyroid drugs is not advocated due to alterations happening from the underlying disease itself (8). Cholestasis may occur in patients with hyperthyroidism. Bile transport is interfered with due to the increase of hepatic oxygen consumption but without an increase of hepatic blood flow thus lowering the oxygen tension in the centrilobular zone (9).

Thyroxine also can cause cholestasis directly. Of note, alkaline phosphatase (ALP) is not of a significant value in assessing hyperthyroidism/ATD induced liver insult as its rise can be simply correlated to the Thyroxin induced increase in the osteoblastic activity (10). Autopsies in patients with hyperthyroidism demonstrate hepatic inflammation, fibrosis, and centrilobular necrosis. Organ oxygen consumption but not blood flow augments with the increase of the metabolic rate. The arteriovenous oxygen difference across the splanchnic bed increases, and hypoxia causes hepatic injury (11).
The estimated incidence of antithyroid agent’s associated hepatotoxicity is about 0.5%. PTU was reported to cause 23 liver transplants from 1990 to 2007 in the US and was ranked as the third most common cause of drug-induced liver failure requiring transplants (12). A transient increase in AST and ALT levels is observed in 30% of patients taking Propylthiouracil which usually normalizes 6 weeks plus from treatment initiation (13).

In one report, 389 patients receiving either PTU or MMI were studied. The adverse effects included five patients developing hepatotoxicity. Four out these five were treated with PTU and one with low-dose MMI (7).

ATD induced liver injury is thought to be based on an allergic host response. PTU triggers a cell mediated immune reaction. Lymphocytic sensitization occurs with subsequent release of cholestatic factors. Both carbimazole and propylthiouracil differ in their mechanisms of causation of liver damage. CMI, being a sulphonamide, triggers an allergic reaction, which can lead to cholestatic jaundice as well as pancreatitis, erythema nodosum and type 2 DM.

The clinical presentation of patients with MMI-induced hepatotoxicity is similar to that of PTU, with patients presenting with symptoms of jaundice, fatigue, pruritus and malaise. However, it is known that MMI causes less severe liver toxicity, so the patients may not be as critically ill on presentation and may not progress to the severity of illness induced by PTU. CMI causes elevation of ALT by 2-3 folds; however, this 2-3-fold rise is not a recommendation to stop the treatment. Rather close monitoring should be done. If the rise is more than 3 fold up the upper normal limit then the drug should be stopped. Of note, liver enzymes keep rising for 1 week after stopping CMI then start to drop gradually returning back to normal by 6-8 weeks. Liver enzymes take about 5 month to normalize in case of PTU induced liver injury.

**CONCLUSION**

Confirmation of carbimazol induced liver injury (CMI) is made by the routine workup of drug induced liver injury. Drug induced liver injury workup entails proper history taking regarding the offending drug administration as well as use of any concomitant drugs. Exclusion of other causes of liver injury/cholestasis, dechallenge and rechallenge. Liver biopsy, although is not a must in all cases, remains the most confirmatory tool for CMI induced hyperbilirubinemia. Because cholestatic pattern is the most common clinical finding; biopsy of the liver is most likely to show expanded portal tracts with inflammatory cells. Proliferating cholangiocytes and bile plugs can also be seen. Diffuse swelling of hepatocytes is another feature that can be seen (14,15).

**ETHICAL APPROVAL**

A written informed consent was obtained from the patient for publication of this case report.

**CONFLICT OF INTEREST**

The authors declare no conflicts of interest