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Case Report

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CARBIMAZOLE INDUCED CHOLESTATIC HEPATITIS: A CASE REPORT

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ABSTRACT

Background: Carbimazole, the most commonly used drug to treat the hyperthyroidism. Hepatitis induced by anti thyroid agents is very rare and drug specific. **Case report:** A 28-year-old unmarried woman presented to the hospital with the complaints of fever, yellowish discolouration of eyes and reduced appetite since 15 days. On examination, her vitals were normal, moderate icterus, bilateral pitting pedal oedema and mild tenderness in the hepatic region observed and negative past history of chronic conditions. Her past medical history revealed that she was a known case of hyperthyroidism and on T.carbimazole 10mg thrice daily for the previous 15 days. She was neither a smoker nor alcoholic and not a drug abuser. Since there was no evident cause for her cholestatic hepatitis apart from the drug, diagnosis of Carbimazole induced hepatitis confirmed. The cholestatic hepatitis was managed by liver protectants along with multi vitamins and hyperthyroidism by lithium, following the withdrawal of the offending drug carbimazole. **Conclusion:** It is essential for health care professionals to be aware of the importance of monitoring hepatitis and liver function in all patients those who are consuming any type of anti-thyroid drugs especially thionamides.

KEYWORDS: Hyperthyroidism, Thionamide, Carbimazole, Cholestatic hepatitis.

INTRODUCTION

Hyperthyroidism is the most common disease across the globe with an incidence of 0.1 per 1000 men and 0.4 per 1000 women. In India, around 42 million people suffered from different thyroid disorders.[1] Carbimazole is the most commonly used drug to treat the hyperthyroidism, because of its longer intra-thyroidal half-life than in plasma and superior safety and efficacy. The incidence of drug induced liver injury (DILI) has been observed as 14 to 24 per 100000 inhabitants.[2] The main drugs concerned were anti infectious, psychotropic, hypolipidemic agents and non-steroidal anti-inflammatory drugs (NSAIDs). Hepatitis induced by anti thyroid agents is very rare and it is drug specific. We express our experience of managing a case of acute cholestatic hepatitis secondary to Carbimazole.

CASE REPORT

A 28-year-old unmarried woman presented to the hospital with the complaints of fever, yellowish discolouration of eyes and reduced appetite since 15 days. On examination, her vitals were normal, moderate icterus, bilateral pitting pedal oedema and mild tenderness in the hepatic region observed and negative past history of chronic conditions. Cholestatic hepatitis was suspected based on the symptoms. The hepatitis serology was negative for hepatitis A, B and C. Since anti-nuclear antibody result found to be negative, suspicion of hyperthyroidism induced hepatitis was omitted. Approximately, a four times elevation in liver parameters were observed (Total bilirubin=24.82mg/dl, indirect bilirubin=13.78mg/dl, AST=152 U/L, ALT=84 U/L and ALP= 542 U/L). Ultrasonography of abdomen reveals mild ascites and left pleural effusion.

Then the case was further referred to clinical pharmacy department to rule out any drug involvement. Past medical revealed that she is a known case of hyperthyroidism and on T.Carbimazole 10mg thrice daily (TID) for the previous 15 days. She was neither a smoker nor alcoholic and not a drug abuser. A detailed literature review was conducted and time temporal relation was assessed. Since there was no evident cause for her cholestatic hepatitis apart from the drug, diagnosis of carbimazole induced hepatitis confirmed.

The physician started on medications Tab.Ebastine 10mg OD, Cholestyramine 5mg TID and Ursodeoxycholic acid 150mg BD along with multi-vitamins OD to prevent further insult to the liver followed by the withdrawal of offending drug carbimazole.

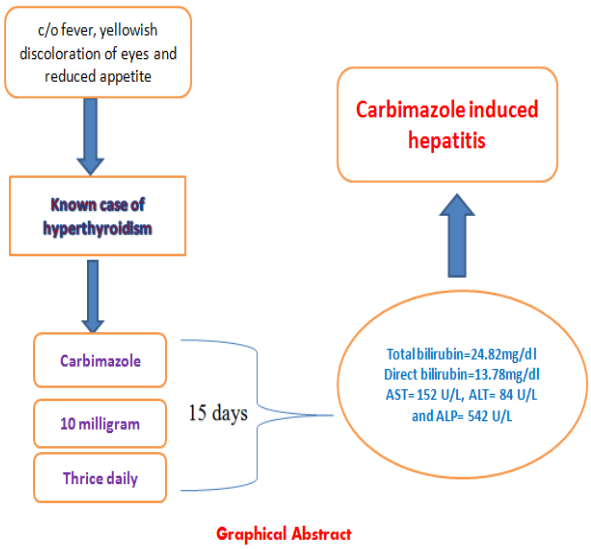

Figure 1: Graphical abstract of case.

She was referred to an endocrinologist for management of hyperthyroidism and started on Tab. Lithium 250mg BD and propranolol 10mg TID. Her LFT and thyroid level was monitored weekly and became near normal after four weeks. So she was well stabled with the treatment of liver protectants and lithium for hyperthyroidism. The patient was discharged on Lithium and propranolol along with liver protectants and advised to review after one week.

During her next follow-up liver biopsy (transjugular) was planned in view of various factors which prognosticate the disease, but the patient refused. Our patient was improving with treatment for hepatitis. The liver function test and thyroid functions were routinely monitored (Table 1).

Table 1: Week wise lab parameters of the patient.

PARAMETER	Normal	At admission	Week 1	Week 2	week 3	Week 4
Alb (g/dl)	3.5-5	-	1.95	2.4	2.16	2.51
T P (g/dl)	5.5-9.9	-	5.52	5.18	4.89	4.15
A/G	1.2-2.5	-	0.9	0.9	0.8	1.5
AST (U/l)	12-38	152	291	283	110	50
ALT (U/l)	7-41	84	86	72	50	34
ALP (U/l)	37-306	542	347	260	229	196
TB (mg/dl)	0.3-1.3	24.82	24. 47	-	23.24	19.13
DB (mg/dl)	0.1-0.4	11.04	16.54	-	16.23	16.17
T3 (pg/ml)	2.3-4.2	-	1.77	4.88	4.50	3.42
T4 (ng/dl)	0.8-2.7	-	10.96	-	3.6	2.26
TSH (µU/ml)	0.27-4.2	-	0.005	-	-	0.005

TP: Total protein; A/G: Albumin/globulin ratio; AST: Aspartate aminotransferase; ALT: Alanine transaminase; ALP: Alkaline- phosphatase; TB: Total bilirubin; DB: Direct bilirubin; T3: Triiodothyronine; T4: Thyroxine; TSH: thyroid-stimulating hormone.

ASSESSMENT OF ADR

The causality assessment of ADR was done using both WHO' causality assessment algorithm and Naranjo's scale. Based on a time-temporal relationship and the reaction unlikely attributed to other medication, but there is a possibility of hyperthyroidism induced hepatitis. So, it was possible according to the WHO scale and same with Naranjo's scale with a score of 4.

DISCUSSION

Antithyroid property of thionamides can be explained by their longer thyroidal half-life compared to plasma half-lives. Methimazole appears to have a plasma half-life of 6.8 hours, whereas, about 20 hours in thyroid tissue followed by oral administration.[3] Carbimazole (CBZ) is better than propylthiouracil (PTU) due to its higher compliance rates, and not as much of toxicity, particularly when prescribed in lower doses.[4] This has led to the suggestion that CBZ should be the first-line drug when pharmacologic treatment for hyperthyroidism is initiated.

Hyperthyroidism causes a mild elevation in the liver enzymes that normalizes with treatment and cholestatic jaundice can occur solely when hyperthyroidism is severe. All antithyroid drugs (methimazole, CBZ and PTU) can have an effect on the liver rarely. In our case, a negative screening test for antinuclear antibody was seemingly against the judgment of autoimmune hepatitis. So, it is an evidence that the reaction most likely drug-induced. Substitution of PTU for CBZ was the next option, but not initiated keeping in mind the likelihood of PTU induced hepatitis. PTU is the third most widespread root of drug-related liver failure and accounts for 10% of the drug-related liver transplantation[5]

Our patient put on liver protectives like cholestyramine, ursodeoxycholic acid and multi vitamins. Her liver functions monitored closely to make out the improvement after drug stoppage and treatment. Endocrinologist proceeds with stopping of the plausible antithyroid drug (CBZ) causing hepatitis and replacing it with other medications like lithium for hyperthyroidism and propranolol to control the secondary symptoms of

hyperthyroidism. Lithium as such is not a treatment option for the hyperthyroidism, but it is having an effect of hypothyroidism. Based on this effect, we decided to go with lithium with continuous monitoring of side effects which may arise due to lithium. When we monitored the liver functions of our patient noticed that her liver functions were improving despite treatment and also T4 became near normal after 4 weeks.

Since the antinuclear antibody was negative, the possibility of involvement of other auto-immune hepatitis was precluded. But, there is a possibility that hyperthyroidism may attribute to hepatitis. Also, notice that patient refused to do the biopsy so that we were limited to find more other factors which may relate to the condition. So, the reaction is assessed as possible according to WHO and Naranjo's scale.

CONCLUSION

It is essential for health care professionals to be aware of the importance of monitoring hepatitis and liver function in all patients those who are consuming any type of anti-thyroid drugs especially thionamides. Switch over or stopping of offending drug and provide symptomatic treatment along with the adequate liver function monitoring.

ABBREVIATIONS USED

BD: twice daily; OD: once daily; TID: thrice daily; Inj: Injection; Tab: Tablet; LFT: Liver function test; ALT: Alanine transaminase; AST: Aspartate aminotransferase; ALT: Alkaline- phosphatase; mg: milligram; PTU: propylthiouracil; U/l: Units/litre; g/dl: grams/deciliter; pg: picogram; ng: nanogram: µU/ml: microunit/millilitre

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