

Agranulocytosis: A Rare Complication and Management Paradox

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Case Report

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Abstract

Introduction: Thyroid disorders are common disorders seen around the globe. The prevalence of thyroid disorders in India is approximately 5-10%, more common in females and hypothyroidism being more common than hyperthyroidism followed by hyperthyroidism. Anti-thyroid drugs are commonly used for the medical management of hyperthyroidism. A rare and notoriously dangerous complication of these drugs is agranulocytosis, seen in 0.3-0.5% of treated patients.

Case: A 50 year old female presented in the emergency department with high grade fever associated with rigors and severe throat pain associated with difficult and painful swallowing since 5 days. She was a known case of hyperthyroidism on carbimazole 30 mg once daily since 1 year. Patient was vitally stable and throat examination showed severely enlarged and inflamed tonsils with inflamed posterior pharyngeal. ENT opinion was taken which advised for conservative management and elective tonsillectomy later. The entire fever profile was negative. Her total leucocyte count was 650 cells/mm³. Carbimazole induced agranulocytosis was suspected and the drug was withheld. Gradually the WBC count started to rise and patient recovered symptomatically.

Conclusion: Agranulocytosis is a potentially lethal side effect but if diagnosed early is treatable. High index of suspicion and timely drug withdrawal is the key to reduce morbidity and mortality.

Keywords: Hyperthyroidism; Agranulocytosis; Carbamazole

Introduction

Thyroid diseases are one of the most common endocrine disorder worldwide having higher prevalence

in females [1]. As shown in several epidemiological studies the prevalence of hyperthyroidism was either subclinical or overt hyperthyroidism and was present in 1.6% and 1.3% of the population [2]. Thionamide group

of drugs were discovered way back in 1943 to treat hyperthyroidism which inhibits thyroid hormone synthesis. They are actively transported into the thyroid gland by $\text{Na}^+ - \text{I}^-$ symporter, where they inhibit both the organification of iodine to tyrosine residues in thyroglobulin and the coupling of iodothyronines [3]. Propylthiouracil, carbimazole and methimazole are the thionamide drugs available and commonly used. These drugs act like a double edged sword as they treat hyperthyroidism a life threatening condition and may increase mortality and morbidity with its dangerous side effects like agranulocytosis. Hereby we report a case of 50 year old female who presented in neutropenic sepsis probably secondary to carbimazole induced agranulocytosis.

Case Report

A 50 year old female a known case of hyperthyroidism on tablet carbimazole 30mg once daily since 1 year, presented in the emergency room with complaints of high grade fever with rigors, severe throat pain, painful swallowing and loose stools since 5 days. She had no other comorbidities. On examination of the throat she had bilaterally enlarged and inflamed tonsils, with congested posterior pharyngeal wall (Figure 1). Systemic examination was unremarkable with Watsky score of 20. All routine blood investigations were sent including blood and throat swab cultures and are described in Table 1 and Table 2.

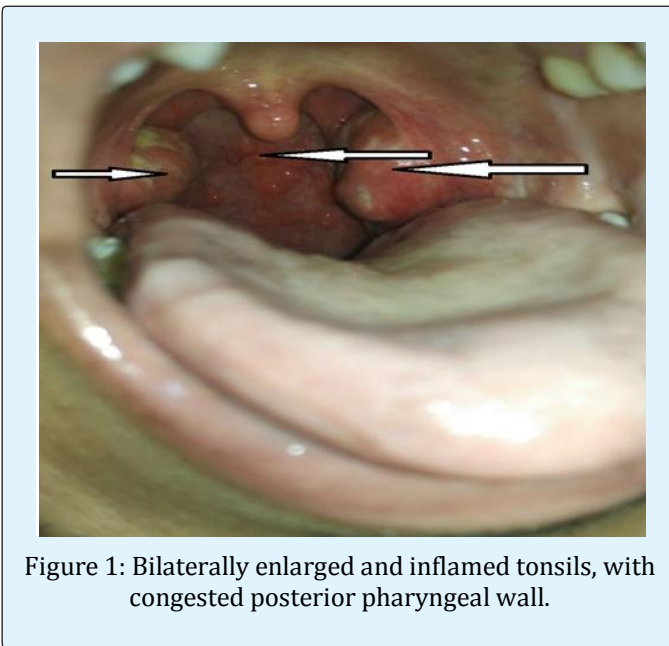


Figure 1: Bilaterally enlarged and inflamed tonsils, with congested posterior pharyngeal wall.

Investigation	Report
Heamoglobin	12.1 g/dl
PLATELETS	1.45
Erythrocyte Sedimentation Rate	108
Malaria Parasite	NEGATIVE
DENGUE	NEGATIVE
T3	95.4 g/ml
T4	8.4 $\mu\text{g/ml}$
TSH	< 0.01 $\mu\text{IU/ml}$

Table 1: Base Line investigations.

Investigation	Report
Peripheral smear	Severe leucopenia with marked neutropenia, reactive lymphocytosis and relative eosinophilia.
Throat swab culture and sensitivity	Gram stain: few pus cells, few gram negative & gram negative bacilli seen. Organism: Klebsiella pneumoniae.
USG neck	Few enlarged lymph nodes bilaterally in levels 2, 3, 4, largest measuring 1.4 cm. Right lobe of thyroid showed a cyst measuring 3mm normal in vascularity.

Table 2: Special Investigations.

Treatment and Outcome

Patient was isolated and reverse barrier nursing was initiated. Carbimazole was withheld immediately. Patient was started empirically on injectable cefoperazone and sulbactam 1.5 gm twice daily, injection metronidazole 500 mg thrice daily. Paracetamol was given for fever spikes and chlorhexidine mouthwash for oral congestion. On symptomatic treatment patient WBC's showed increasing trend as described in Table 3 and patient got relieved symptomatically. Then patient was advised radio iodine ablation and was discharged only beta blockers.

	Day 1	Day 3	Day 7
WBC Count	650	2610	6150

Table 3: White Blood Cells (WBCs) Increasing Trend.

Discussion

Carbimazole, a prodrug which gets converted into the active form methimazole. It is used alone or in combination with other medications for the treatment of

hyperthyroidism. This therapy usually started with two to three divided doses in total of 30–60 mg/day but the maximum daily dose should not exceed 120mg. usually within 4–8 weeks of starting therapy, symptoms will diminish and circulating thyroid hormone levels will return to normal. Typical range of daily maintenance dose in adults is 5–30 mg/day. The serum half-life of carbimazole is five to six hours but have prolonged half-life intra thyroid. Thionamides like methimazole, carbimazole and propyl thiouracil may cause minor side effects like pruritus, rash, urticaria, arthralgia, arthritis, fever, abnormal taste sensation, nausea, or vomiting in up to 13 percent of patients [4]. But some of the serious side effects are agranulocytosis and hepatotoxicity. The incidence of carbimazole induced agranulocytosis is 0.3–0.6% [5] and has got a mortality rate of 21.5% [6]. In 1983, a study conducted by Cooper et al. concluded that methimazole in higher doses of 30 mg/day and age of 40 years or above caused greater risk for the development of agranulocytosis [7]. Drug-induced agranulocytosis usually occurs within 1–2 months of taking the anti-thyroid medication but the onset in some cases may get delayed, like in our case patient developed agranulocytosis after being on carbimazole for one year. Over a period of 1–2 weeks, the WBC count usually returns to normal after discontinuing the offending drug and the time taken can be estimated between days to months [8,9]. The mechanism behind agranulocytosis is considered to be immune mediated destruction of granulocytes and idiosyncratic drug reactions. Successful treatment of anti-thyroid drug-induced agranulocytosis by GCSF (granulocyte colony-stimulating factor) has been reported [10]. It enhances the recovery of the peripheral blood granulocyte lineage which results in the faster normalization of peripheral granulocyte count as well as reduction in chances of fatal complications like bacterial infections [11].

Conclusion

Thionamides are used to treat hyperthyroidism and hyperthyroid patients started on anti-thyroid medications, should be warned about the dangerous side effects, not only on initiation of the medication but on every follow up visit as well. Patients taking anti thyroid medications presenting with high grade fever with neck discomfort, agranulocytosis should be suspected and timely investigations are required to confirm. Here the treatment has paradox in form of withholding medications instead of prescribing medications with symptomatic support.

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