Case Report

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A life-threatening case of drug-induced agranulocytosis

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ABSTRACT

A 26 year old hyperthyroidic female with prescribed carbimazole intake from 1 month presented with intermittent low grade fever, sore throat and dysphagia since last 15 days. She appeared very weak and pale. On clinical evaluation, TLC was found very low and DLC showed decreased neutrophil percent. Carbimazole was suspected as the cause and immediately stopped. G-CSF (Filgrastim) was started along with other conservative management and TLC started to rise gradually. On 12th day from admission, she developed acute pain abdomen and diagnosed as having intestinal perforation for which she was immediately operated but unfortunately expired 6 hours after surgery. Drug-induced agranulocytosis can be so fatal that if not diagnosed and treated early, can lead to death due to its widespread rapid systemic derangement.

Keywords: Carbimazole, Agranulocytosis, Grave's disease

INTRODUCTION

Carbimazole is an anti-thyroid drug mainly indicated for rapid resolution of hyperthyroid symptoms, works by inhibiting thyroxine hormone production in the thyroid gland. A total of 30-60 mg can be advised per day with a maximum dose not exceeding 120 mg. Within 4-8 weeks, symptoms diminish and circulating thyroxine levels return to normal. Side effects associated with this drug are pruritic rash (most common), fever, urticaria, arthralgia, hepatitis and most serious agranulocytosis. If higher doses are taken by the patient, chances of agranulocytosis are high and can happen within 2 months of therapy.

CASE REPORT

A 26 year old female with obvious neck swelling (Figure 1) diagnosed as grave's disease and on treatment with carbimazole since 1 month presented with complaints of sore throat and fever since 15 days. On examination, multiple oral mucosal ulcerations found over palate

(Figure 2), tonsils, uvula and posterior pharyngeal wall. Tongue was coated white with dirty slough and tonsils were found to be enlarged with whitish-grey membrane. Thyroid swelling was diffuse, smooth surfaced, having rounded borders and no palpable nodularity. Jugulodigastric nodes were palpable on both sides. Mild pallor noted.



Figure 1: Patient presentation.

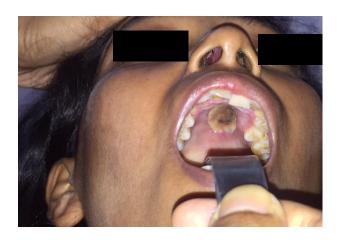


Figure 2: Ulcer over palate.

Patient was admitted and on investigation, total leucocyte count was found as 600/mm³. Carbimazole was stopped immediately and conservative management given. 6 mg of Filgrastim (G-CSF) given subcutaneously for neutropenia. Throat swab showed growth of *Klebsiella* and appropriate sensitive antibiotic (piperacillin+tazobactam) started. Thyroid profile showed hyperthyroidism (Table 1). Ultrasound neck showed diffuse thyromegaly with increased vascularity suggesting Grave's disease and bilateral enlarged jugulo-digastric nodes. FNAC showed hyperplastic thyroid follicular cells

with mild anisonucleosis and arranged in micro acinar pattern (Figure 3) suggesting a possibility of hyperplastic adenomatous goitre and follicular neoplasm but not confirmatory.

Table 1: Thyroid function tests.

Thyroid function tests	05/03/2018	09/03/2018
Total T3 (nmol/L)	3.30	3.61
Total T4 (nmol/L)	151	225
TSH (mIU/L)	< 0.015	< 0.015

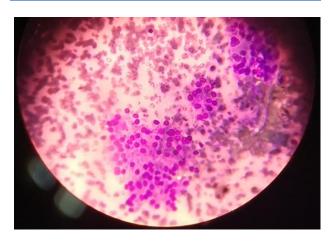


Figure 3: FNAC.

Table 2: Variation of blood parameters during hospital stay.

Haematological	05/03/18	08/03/18	10/03/18	14/03/18
Hb (g%)	8.1	7.7	8.1	6.6
TLC (/mm ³)	600	1000	1300	2600
DLC	N-15%, L-84%	N-6%, L-88%	N-12%, L-84%	
ESR (mm)	120	140		

A diagnosis of primary hyperthyroidism (Grave's) and carbimazole induced agranulocytosis was made. Also included are membranous tonsillitis, pharyngitis and aphthous ulceration for which neutropenia was suspected as the cause.

Despite adequate antibiotic therapy, treatment of leukopenia by administration of colony stimulating factors and management of anaemia by blood transfusion, patient failed to respond and neither pharyngitis nor oral ulcerations were resolved. Only leucocyte number was slowly accelerating (Table 2), but not as expected. She was febrile during whole period of treatment and was suffering from odynophagia.

On 12th day from admission, she suddenly developed severe abdominal pain associated with vomiting. Patient was evaluated by concerned department and diagnosed as intestinal perforation. Neutropenia induced enterocolitis was suspected as the cause. Patient was immediately posted for surgical intervention and primary repairing of perforation with exploratory laparotomy and ileostomy

was done under GA. Also one unit of blood transfused on-table. Unfortunately, patient expired 6 hours after surgery while in post-op ICU.

DISCUSSION

Drugs of choice for hyperthyroidism include anti-thyroid drugs (thionamides—carbimazole, propylthiouracil). Other treatment forms include radioactive iodine and surgery.

Advantages of thionamides include rapid symptom relief and inexpensive. Disadvantages are long course of treatment (12-18 months), high chance of relapse and life-threatening agranulocytosis.

Incidence of agranulocytosis is 0.3-0.6% and mortality rate among them is 21.5%.^{3,4} It can occur at any point of time after treatment without any specific warning signs, most commonly within 1-3 months after therapy as occurred in our patient. According to available guidelines in literature, patient should stop the drug immediately if any features of sepsis occur and thyroid parameters should be monitored every 4 to 6 weeks.⁵ In our case,

patient was unable to identify the features of sepsis which may be due to lack of proper education regarding safety profile of the drug. Hence this signifies the importance of proper patient education.

If identified early and stopped immediately, WBC count can revert to normal in 1-2 weeks depending on age, comorbidity, duration, immediate antibiotic therapy. As our patient presented late (i.e., after 15 days) and with associated severe comorbidity, even a prompt diagnosis and swift management was unable to save her.

Sprikkelman et al described possible cause of agranulocytosis could be that antibodies produced on binding of drug to granulocyte self-destructs thinking it as a foreign antigen.⁷

Successful treatment of anti-thyroid drug-induced agranulocytosis by G-CSF (granulocyte colony-stimulating factor) has been reported. 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. In our case, severe co-morbid conditions of the patient outweighed the gradual improvement in the neutrophil count. Also rapid rise in neutrophil count was not seen. Probably an early presentation to the hospital would have been much better.

CONCLUSION

Antithyroid drugs whenever administered should be given with utmost caution and patient should be warned accordingly. Early presentation combined with prompt diagnosis and effective management can have a better prognosis. Patient should be educated in detail regarding the serious adverse effects of the drug and should be asked to report immediately in case of suspicion.

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REFERENCES

- 1. Mohan A, Joseph S, Sidharthan N, Murali D. Carbimazole-induced agranulocytosis. J Pharmacol Pharmacothera. 2015;6(4):228-30.
- Cooper DS, Goldminz D, Levin AA, Ladenson PW, Daniels GH, Molitch ME, et al. Agranulocytosis associated with antithyroid drugs. Effects of patient age and drug dose. Ann Intern Med. 1983;98:26–9.
- Genet P, Pulik M, Lionnet F, Bremont C. Use of colony stimulating factors for the treatment of carbimazole-induced agranulocytosis. Am J Hematol. 1994;47:334–5.
- 4. Juliá A, Olona M, Bueno J, Revilla E, Rosselló J, Petit J, et al. Drug-induced agranulocytosis: Prognostic factors in a series of 168 episodes. Br J Haematol. 1991;79:366–72.
- Joint Formulary Committee. Suggestions for Drug Monitoring in Adults in Primary Care. BNF. 2013; 65.
- Tavintharan S, Rajasoorya C, Chew LS. Carbimazole-induced agranulocytosis-a report of 2 recent cases. Singapore Med J. 1997;38:386–7.
- 7. Sprikkelman A, de Wolf JT, Vellenga E. The application of hematopoietic growth factors in druginduced agranulocytosis: A review of 70 Cases. Leukemia. 1994;8:2031–6.
- 8. Gerl A, Gerhartz H, Wilmanns W. GM-CSF for agranulocytosis. J Intern Med. 1991;230:90–1.
- 9. Sheng WH, Hung CC, Chen YC, Fang CT, Hsieh SM, Chang SC, et al. Antithyroid-drug induced agranulocytosis complicated by life-threatening infections. QJM. 1999;92:455–61.

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