A Case of Graves' Disease with Rare Complication of Carbimazole Induced Pancytopenia

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ABSTRACT

Introduction: Pancytopenia, potentially a life threatening condition is a rare manifestation of Graves' disease and can occur due to many causes. Antithyroid drug therapy being one of the important cause, is associated with serious adverse effects like agranulocytosis and aplastic anemia. Early recognition and management of this serious complication is important.

Case Report: We report a case of Graves' disease in an adult male on carbimazole, who developed pancytopenia, two years after restarting the therapy after an initial treatment of four years. He recovered completely after withdrawing the offending agent, along with blood transfusion and haematinics treatment. Subsequently he underwent radioactive iodine ablation as a definitive treatment for Graves' disease.

Conclusion: Early recognition of pancytopenia in a patient of Graves' disease on antithyroid medication is important to prevent complications. Radioactive iodine ablation therapy or thyroid surgery are preferred in them, as other antithyroid medications are contraindicated.

Keywords: Pancytopenia, Antithyroid Medication, Carbimazole, Radiactive Iodine Ablation

INTRODUCTION

Pancytopenia is a condition characterized by a decrease in the number of all three formed elements of blood, namely red blood cells, white blood cells and platelets.[1] It results from primary or secondary involvement of bone marrow by various disease processes. Drugs are the most common cause of pancytopenia.[2] Drugs can cause pancytopenia by different mechanisms, such as bone marrow suppression by cytotoxic medications, dose related effects as in chloramphenicol or immune mediated as in non steroidal anti inflammatory drugs.[1] Antithyroid medications cause pancytopenia by immune mediated mechanisms. Agranulocytosis is the more common hematological abnormality occurring in 0.1-0.5% of patients taking anti thyroid medications, whereas pancytopenia is very rare.[3] We report a case of Graves' disease in an adult male, who developed pancytopenia while on long term carbimazole therapy.

CASE REPORT

A forty eight years old male, was diagnosed as a case of Graves' disease in 2011 and was instituted carbimazole therapy, which he discontinued in 2015. He presented to endocrinology out patient in Feb 2017 with history of diffuse goiter and toxic features in the form of weight loss, tremulousness, excessive sweating and palpitations. Technetium 99 thyroid scan of the thyroid showed diffuse uniform enhanced uptake (Figure-1).

As there was failure to achieve remission by antithyroid drugs treatment, patient was advised to undergo either radioactive iodine ablation or surgery as a definitive therapy, both of which he declined and insisted on continuing anti thyroid medication and hence was restarted on carbimazole 30mg/day, later reduced to 10 mg/day. While on regular follow up, he reported in Mar 2019 with complaints of mild yellowish discoloration of eyes, mild swelling of lower limbs and tiredness of three weeks duration. He denied any history of fever, sore throat, abdominal swelling, oliguria, chest pain, palpitations, orthopnea or similar episodes in the past. He was taking carbimazole regularly but denied any alternative system of treatment. He had no family history of thyroid disease or allergy.

On Examination: Temperature-37^{0}C, pulse-92/min, regular. B.P.-130/80 mmHg, height-166cm, weight-63kg, BMI-23.68 kg/m^2. There was a non tender, firm, diffuse goiter with regular borders and without any retrosternal extension. On auscultation over thyroid, faint bruit was heard. He had pallor, mild icterus, bilateral minimal pedal edema, with no evidence of purpura or ecchymosis. Hemic flow murmur was heard over pulmonary area. There was no ascites or organomegaly. Rest of systemic examination was normal. Investigations are presented in table-1.

Patient was hospitalized, carbimazole immediately stopped and propranolol was continued. Patient was transfused two units of blood, haematinics were added to therapy and discharged from hospital on beta blockers and hematinics. Review after one month revealed that the patient had improved, jaundice subsided and appetite was better. He had a sense of well-being. Repeat blood tests showed normalization of total leucocyte count and bilirubin levels. Subsequently he underwent radioactive iodine ablation as a definitive treatment for Graves' disease He was counseled about hypothyroid features and asked to do follow up in OPD

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How to cite this article: KM Suryanarayana. A case of graves' disease with rare complication of carbimazole induced pancytopenia. International Journal of Contemporary Medical Research 2020;7(2):B1-B3.

DOI: http://dx.doi.org/10.21276/ijcmr.2020.7.2.43

Parameters	31/03/ 2019	04/04/2019	06/04/2019	30/4/2019
Haemoglobin (g/dL)	5.6	6.3	7.9	10.5
WBC (cells/mm^3)	2650	2720	2760	5680
Neutrophils (%)	58	55	52	56
Lymphocytes (%)	34	37	38	34
Eosinophils (%)	03	04	05	07
Basophils (%)	05	04	05	03
Platelets (lakh/mm^3)	0.53	0.67	0.75	1.45
ESR (mm/h)	89	79	58	43
LFT				
Total bilirubin (mg/dL)	2.01	1.21	0.95	
Direct bilirubin (mg/dL)	0.77	0.60	0.45	
Total protein (gm/dL)	5.7	5.2	5.4	
Albumin (gm/dL)	3.2	2.9	3.2	
SGOT (IU/L)	34	20	16	
SGPT (IU/L)	32	15	13	
Alkaline Phosphatase (IU/L)	82	78	96	
GGT (IU/L)	12	13	13	
Blood Urea (mg/dL)	8.9			
Serum Creatinine (mg/dL)	0.5			
TSH - < 0.005 uIU/mL (0.35-4.94); T4 – 113 nmol/l (65-131); Coomb's test: Direct and indirect – Negative; Serum vitamin B 12 level – > 2000 pg / mL (deficiency < 150); Serum folic acid – > 20 ng / mL (deficiency < 3); Serum LDH – 1592 U / L (140-280); Anti-nuclear antibody – Negative; Blood group – B positive				

Table-1: Investigations

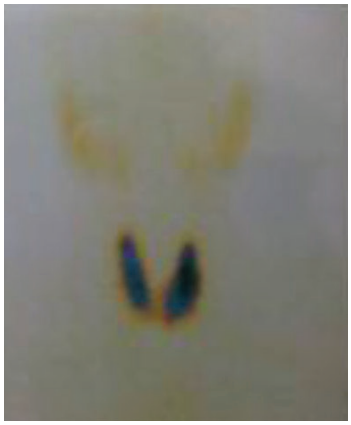

Figure-1: Technetium 99 thyroid scan showing diffuse uniform increased uptake

after 8-12 weeks for further treatment. He was instituted thyroxine replacement subsequently, after he was confirmed to have developed post ablation hypothyroidism.

DISCUSSION

Pancytopenia is a rare manifestation of Graves' disease and can occur by various mechanisms. Hyperthyroidism itself can cause pancytopenia.[4] But as evident from the reports in this case, patient had normal T4 at the time of presentation although TSH was suppressed. Graves' disease can be associated with autoimmune hematological conditions like hemolytic anemia or pernicious anemia which causes pancytopenia.[5] 1-3% of Graves' patients can have pernicious anemia.[6] This patient had normal levels of vitamin B12, which rules out pernicious anemia. The third mechanism is antithyroid medication induced pancytopenia. Antithyroid medications commonly cause agranulocytosis. However pancytopenia is rare with only 42 cases reported in literature till 2011.[7] In another retrospective Japanese cohort study of agranulocytosis and pancytopenia involving 50385, only 5 patients developed pancytopenia The median value and range of cell counts at the onset of pancytopenia in the five pancytopenic patients were WBC 900/μL (200-2700/μL), granulocyte 4/μL (0-108/μL), Hb 9.3 g/dL (9.1-11.0 g/dL) and platelet 89 × 103 /μL (36-100 ×103 /μL).[7] Amongst various antithyroid medications methimazole is specifically cited to cause pancytopenia.[8] In our case we report pancytopenia due to carbimazole.

Various mechanisms mentioned above have significance in management. Hyperthyroidism causing pancytopenia responds to treatment with antithyroid medications, whereas anti thyroid medication causing pancytopenia requires stoppage of medications. Hence a clear etiological mechanism needs to be established before embarking on therapy. Most of the antithyroid medications cause bone marrow damage in first 3 months but agranulocytosis occurring up to 1 year after treatment is reported.[9] However in the present case pancytopenia occurred after 2 years of retreatment with carbimazole. Treatment with other antithyroid medications is contraindicated due to cross reactivity.[10] Various treatment strategies include - stopping the offending medicine, prevention of infection and hematinic support. Rarely granulocyte colony stimulating factor may be required. In severe cases of aplastic anemia, antithymocyte globulin or cyclosporine may be given.[1]

CONCLUSION

Early recognition, evaluation and treatment of pancytopenia, a potentially life threating condition in a Graves' disease patient on antithyroid medication is necessary. Such a patient should be advised to undergo radioactive iodine ablation therapy or surgery, as treatment with other antithyroid drugs is contraindicated.

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Source of Support: Nil; **Conflict of Interest:** None

Submitted: 02-01-2020; **Accepted:** 08-02-2020; **Published:** 29-02-2020