

Pancytopenia in a Patient with Grave's Disease

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SUMMARY

Pancytopenia can rarely complicate Grave's disease. It can be due to uncontrolled thyrotoxicosis or as a result of rare side effect of antithyroid medication. Pernicious anemia leading to Vitamin B12 deficiency is another rare associated cause. We report a case of a patient with Grave's disease and undiagnosed pernicious anemia whom was assumed to have antithyroid drug induced pancytopenia. Failure to recognize this rare association of pernicious anemia as a cause of pancytopenia had resulted in delay in treatment and neurological complication in our patient.

KEY WORDS:

Grave's disease, Pancytopenia, Pernicious Anemia, Vitamin B12 deficiency, Neurological complication

CASE REPORT

A 48 year-old gentleman with long standing Grave's disease presented with giddiness, lethargy and reduced effort tolerance for 3 weeks. Apart from carbimazole 10mg and propranolol 20mg twice daily, he was not on any other medication. He was a chronic smoker of 10 pack years and social alcohol drinker. He had no other medical illnesses. On examination, he was pale, but not jaundiced. He had mild exophthalmos and a small diffuse goiter but was clinically euthyroid. There was no hepatosplenomegaly. Examination of the cardiovascular and respiratory systems yielded no abnormalities.

Full blood count showed pancytopenia, with normochromic normocytic anemia [hemoglobin of 8.7g/dL, MCV 87.2fL, MCHC 34.4q/L], total white count of 3,200/uL (Neutrophil count 1,160/uL), and platelet counts of 48,000/uL. Reticulocyte count was 0.87%. Peripheral blood film showed microcytic normochromic red blood cells with anisocytosis, macrocytes and tear drop cells. There was no nucleated red blood cell. There was leucopenia with hypersegmented neutrophils but no blast cells, platelet clumping or giant platelet. Thyroid function and liver function tests were within normal limits except for elevated total bilirubin at 28umol/L with predominantly indirect bilirubinaemia. Coomb's tests were negative for both direct and indirect anti-human globulin tests. Iron studies showed no feature of iron deficiency.

He was transfused with 3 pints of packed cells and was treated as carbimazole-induced pancytopenia. The antithyroid medication was ceased and he received radioactive

iodine treatment for his thyrotoxicosis. He was then started on L-thyroxine replacement when he developed hypothyroidism.

He presented 11 months later with one month history of progressive difficulty in walking. On neurological examination, there were no muscle wasting. His tone and power were normal. Reflexes were normal in his upper limbs but absent in his lower limbs. He was severely ataxic on his feet with loss of proprioception and vibration in his lower limbs but intact sensation to pin prick and light touch. There were no other signs of cerebellar syndrome, such as dysdiadokokinesia, dysmetria and nystagmus. Other examination was unremarkable except for presence of atrophic glossitis.

Full blood count again showed pancytopenia (hemoglobin 8.7g/dL, total white count 3,300/uL, platelet 69,000/uL) with peripheral blood film showing many hypersegmented neutrophils consisting of 23% of the blood film. Lactate dehydrogenase level was raised at 2420u/L (normal 140-180u/L). Thyroid function, renal function and liver function tests were otherwise normal.

A diagnosis of megaloblastic anemia secondary to Vitamin B12 deficiency was made and confirmed by low B12 level of 107pg/mL (normal 211-911pg/mL) with normal folate level 10.5ng/mL (normal >2.8ng/mL). Dietary history excluded nutritional deficiency or alcohol abuse. Oesophagoduodenoscopy showed atrophic gastritis with small pre pyloric ulcer.

He was started on intramuscular cyanocobalamin at therapeutic dose with dramatic resolution of his neurological impairment. One day after starting treatment, he could ambulate with support and four days later he could ambulate independently. Subsequent investigation revealed positive intrinsic factor antibody supporting the diagnosis of pernicious anemia as the underlying cause of his vitamin B12 deficiency.

DISCUSSION

Pancytopenia can complicate Grave's disease and it can be due to different aetiologies. First of all, untreated thyrotoxicosis itself has been associated with pancytopenia, which usually resolves after treatment of thyrotoxicosis¹. Low Boon-Hua reported 17 patients with hyperthyroidism associated with pancytopenia from year 1981 till 2008 and found that all of them had resolved blood counts when they

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achieved euthyroid status with either antithyroid medication or radioiodine therapy. Postulated mechanisms of pancytopenia include reduced production of hematopoietic cells from the marrow¹ and increased destruction or sequestration of mature hematopoietic cells, due to associated hypersplenism^{1,2}.

Another important and potentially life-threatening cause of pancytopenia is due to the rare side effect of antithyroid medication. The incidence of agranulocytosis was reported as 0.1-0.5% whereas thrombocytopenia and anemia are rare³. Watanabe *et al* did a retrospective cohort study of agranulocytosis and pancytopenia involving 50,385 patients with Grave's disease at their hospital and found 50 patients who developed antithyroid drug-induced agranulocytosis but only 5 patients with pancytopenia. They also found that agranulocytosis preceded the development of pancytopenia in 4 of the patients. The mean interval between initiation of antithyroid medication to onset of pancytopenia was 41 days, with the shortest duration of 32 days and longest of 97 days. Out of the 5 patients who had antithyroid drug-induced pancytopenia, 4 of them had recovery of the blood counts within 2 weeks of commencing G-CSF and dexamethasone. In their literature review, there were 42 cases of antithyroid medication-induced pancytopenia reported from 1954 till 2011 with most cases being linked to aplastic anemia⁴. It is believed that the pathogenesis is immune-mediated⁵.

Lastly hematological disorders in patients with Grave's disease can be due to associated autoimmune diseases such as autoimmune thrombocytopenia, autoimmune hemolytic anemia and pernicious anemia. Pernicious anemia is the commonest cause of Vitamin B12 deficiency⁶ and can lead to pancytopenia. It is due to the presence of intrinsic factor autoantibodies, preventing absorption of Vitamin B12 in the stomach. It is reported about 1-3% of patients with Grave's disease have associated pernicious anemia⁷.

In our patient, pernicious anemia leading to Vitamin B12 deficiency is the main cause of pancytopenia. Although an alcohol consumer, there were no features to suggest chronic liver disease causing pancytopenia. Moreover, his folate levels were normal. He did not have hepatosplenomegaly, and was clinically and biochemically euthyroid on both presentations. Drug-induced pancytopenia was a worthwhile thought on the first presentation while the patient was still on carbimazole. However, the blood counts remained low 11 months later despite cessation of antithyroid drug, which suggests that antithyroid medication may not have been the cause. On hindsight, there were clues pointing towards diagnosis of Vitamin B12 deficiency on the first presentation, including the involvement of all cell lines and presence of anisocytosis, macrocytes and hypersegmented neutrophils in the peripheral blood film. Had he been investigated and treated earlier, his neurological complication could have been avoided.

Untreated Vitamin B12 deficiency has been reported to lead to neurological complication in up to 40 % of the patients⁸ with progression from distal lower limb sensory disturbances causing ataxia to spastic paraparesis with major neurological disability. Neurological response to Vitamin B12 replacement most often occurs within first 3 months, and the severity of residual neurological dysfunction post treatment is strongly related to the duration of symptoms⁹. Hence early diagnosis and treatment is critical to ensure a favourable neurological outcome.

CONCLUSION

Pancytopenia can rarely complicate Grave's disease. While drug-induced agranulocytosis and pancytopenia is well known and a feared side effect of antithyroid medication, pancytopenia due to pernicious anemia is a less well known association with Grave's disease. Failure to recognize this association had resulted in significant complication and morbidity in our patient. Early recognition and prompt replacement of Vitamin B12 is crucial, not only for the treatment of pancytopenia, but also for prevention of adverse neurological outcome.

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