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Case Report

A rare case of carbimazole induced severe aplastic anemia with fatal outcome

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Abstract

Though agranulocytosis is a well known adverse effect of antithyroid drugs (ATDs), aplastic anemia is thought to be rare. Herein we present a case report of carbimazole induced aplastic anemia in a patient of Grave's disease, who satisfied all the criteria for severe disease and had profound bone marrow hypoplasia. Drug induced aplastic anemia is thought to be a result of an idiosyncratic response directed against hematopoietic stem cells and is managed in a similar fashion to idiopathic aplastic anemia. The hematopoietic damage in our patient did not recover following ATD withdrawal and supportive treatment. This necessitated the use of immunosuppressive therapy with cyclosporine and antithymocyte globulin, which she could not afford and despite of all the supportive treatment she eventually succumbed to severe sepsis. Since ATDs are commonly used in clinical practice, the physicians should be aware of this rare but life-threatening complication.

Keywords: *Antithyroid drugs (ATDs), Aplastic anemia, Carbimazole, Grave's disease, Pancytopenia.*

1. Introduction

Antithyroid drugs (ATDs) have been used as a standard therapy for Grave's disease for more than 50 years. Though well tolerated, ATDs may cause serious life threatening side effects such as agranulocytosis and aplastic anemia. ATDs induced aplastic anemia is a very rare event (Richardson *et al.* 1954, Biswas *et al.* 1991, Escobar-Morreale *et al.* 1997). And hence we report one such case at our centre.

2. Case report

A 50 year old lady presented with complaints of easy fatiguibility, easy bruisablity and bleeding gums for 15 days. She is a known case of Grave's disease on treatment with carbimazole (10mg thrice a day) for the past three months. Physical examination revealed pale skin and mucous membranes, bleeding gums, ecchymotic patches on legs and body. There was no lymphadenopathy and hepato-splenomegaly, other systems being unremarkable. At admission, her blood film revealed pancytopenia with 2.6gm/dl haemoglobin concentration, 0.5×10^9/L leukocytes and severe thrombocytopenia of 2.0×10^9/L. Differential count showed 91% of lymphocytes, 1% of monocytes and 8% of neutrophils. The peripheral smear showed normocytic normochromic picture and absence of blast cells. Absolute reticulocyte count was 20×10^9/L. Bone marrow biopsy revealed severe hypocellularity, replaced with fat cells, iron stores being normal, as shown in Figure. 1. Other tests done such as antinuclear antibody, coombs test, serum iron and cobalamin levels, abdominal ultrasonography, chest radiography, renal and liver function tests, were within normal limits. Review of the past records revealed a normal hemogram before starting therapy with ATDs and a thyroid profile consistent with thyrotoxicosis (TSH- 0.001mcIU/ml, T4-17.6mcg/dl and T3-365ng/dl). She was clinically and biochemically euthyroid during her present hospitalization. Her antithyroid therapy was discontinued and supportive treatment in the form of packed cell and platelet transfusions, colony stimulating factors, prednisolone and barrier nursing was started. No significant hematological recovery was noted and in view of this therapeutic failure she was advised immunosuppression therapy with cyclosporine and antithymocyte globulin, which she refused due to financial constraints. At the end of one month, she was discharged from the hospital at her request. She was counselled regarding her condition and the need for regular follow up. At the time of discharge her hemogram revealed 6.0gm/dl hemoglobin concentration, 2.00 x 10^9/L leucocytes and platelets of 40 x 10^9/L. Differential count showed 78% of lymphocytes, 2% of monocytes and 20% of neutrophils. She followed up regularly at the outpatient department with intermittent hospitalizations for blood transfusions for the next two months, after which she was lost for follow up. One month later patient presented to the emergency room with complaints of fever for three days. On examination, she had pale mucous membranes, bleeding gums, generalized ecchymosis. She had a feeble pulse, blood pressure of 70/50 mm Hg and cold clammy extremities. Breath sounds were normal on auscultation. Hemogram revealed 2.5 gm/dl hemoglobin concentration, 0.4 x 10^9/L leucocytes and severe thrombocytopenia of 2.0 x 10^9/L. Differential count showed 94% of lymphocytes, 3% of monocytes and only 3% of neutrophils. Electrocar-

diogram and chest radiograph were within normal limits. Blood cultures were drawn and broad spectrum antibiotics were started. She was given packed cell and platelet concentrate transfusions, colony stimulating growth factors along with other necessary supportive care. Despite vigorous fluid rescusitation, her shock did not improve, which necessitated the use of inotropes. She eventually succumbed to severe sepsis within 48 hours of admission.

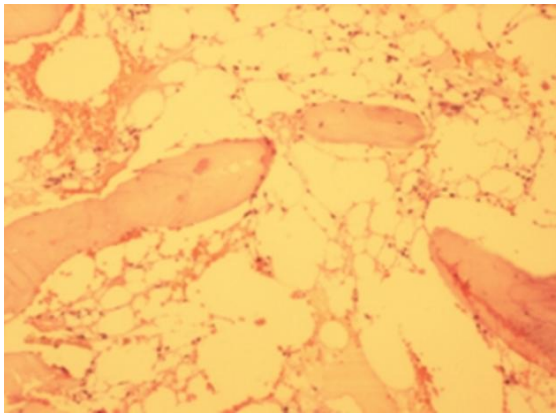

Fig. 1: Bone marrow showing marked hypocellularity and replacement by fat cells.

3. Discussion

Aplastic anemia was first recognized by Ehrlich in 1888. Acquired aplastic anemia is a clinical syndrome in which there is a deficiency of red cells, neutrophils, monocytes and platelets in the blood, and fatty replacement of the marrow with a near absence of hematopoietic precursor cells. The diagnosis usually requires the presence of pancytopenia with neutrophil count fewer than 1.5 x 10^9/L, a platelet count less than 50x 10^9/L, a hemoglobin concentration less than 10gm/dl, an absolute reticulocyte count fewer than 40 x 10^9/L, accompanied by a hypocellular marrow without abnormal or malignant cells or fibrosis (Blood 1987, p. 1718). A bone marrow cellularity of less than 25% and marked decreased values of at least two of three hematopoietic lineages (neutrophil count less than 500/microliter, platelet count less than 20,000/microliter and absolute reticulocyte count of less than 60,000/microliter) defines severe aplastic anemia, as seen in our patient.

Though most of the cases are idiopathic, a plethora of drugs have been implicated as a cause of aplastic anemia. Whether idiopathic or associated with an inciting agent, such as a drug, the reduced hematopoiesis in aplastic anemia results from cytotoxic T-cell mediated immune suppression of very early CD34+ hematopoietic multipotent progenitor or stem cells (Kumar & Goldman 2002).

Occasional cases of aplastic anemia are seen in conjunction with autoimmune diseases. In vitro studies have found either the presence of an antibody or suppressor cell directed against hematopoietic progenitor cells. Severe aplastic anemia also has been reported co-incident with immune thyroid diseases such as Grave's disease and the aplasia has been reversed with treatment of hyperthyroidism (Young *et al. 2006*, Aydin *et al. 2008)*. However this seems to be an unlikely association in our patient, since she was clinically and biochemically euthyroid at the time of diagnosis of aplastic anemia.

When drugs are implicated in causing aplastic anemia, it is important to recognize that unlike agranulocytosis and drug induced thrombocytopenia, stopping the offending drug does not lead to hematopoietic recovery (Williams 1999, p. 1186-1187). Most cases of drug- induced aplastic anemia lead to an idiosyncratic immune response directed against hematopoietic stem cells and are managed similarly to those with idiopathic aplastic anemia. The same was the case with our patient, in whom the hematopoietic damage did not improve following drug withdrawal and our patient eventually succumbed to her illness.

4. Conclusion

This case report emphasizes that ATDs may cause hematopoietic changes, which can be fatal. Since ATDs are commonly used in clinical practice, the physicians should be aware of this rare but life threatening complication.

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