Recovery From Carbimazole-Induced Aplastic Anemia

Wilcox G, Wong R, Elliott PJ, Topliss DJ, Stockigt JR.

Department of Endocrinology and Diabetes, Alfred Hospital, Melbourne, Australia.

We report a case of aplastic anemia developing five weeks after commencement of carbimazole.

A 39 year old woman presented 5 months postpartum, with severe Graves' disease with FT_4 91.9 pmol/L (normal range: 11.0-23.0 pmol/L), FT_3 >32 pmol/L (normal range: 3.0-6.8 pmol/L) and TSH <0.03 mU/L (normal range 0.03-5.00 mU/L). She was treated with carbimazole 15mg tds, range: propranolol 80 mg bd, cholestyramine 4gm qid, and lithium 125mg bd.

She improved clinically within two weeks. FT_4 fell to 27.5 pmol/L and FT_3 to 6.0 pmol/L. Liver function tests and full blood examination were normal. Cholestyramine and lithium were ceased, propranolol was reduced to 20 mg bd and carbimazole to 10 mg tds.

Three weeks later, she presented with a 24-hour history of sore throat, lethargy, vomiting and fever. Carbimazole was ceased within 12 hours of the onset of symptoms. Full blood examination showed Hb 118 g/L, white cell count 0.26 × 10^9/L, platelets 69 × 10^9/L, neut-ronphils 0.03 × 10^9/L, lymphocytes 0.21 ×10^9/L and monocytes 0.00 × 10^9/L.

On admission, she looked unwell, her temperature was 37.7°C and her throat was erythematous, with cervical lymphadenopathy. TSH was <0.03 mU/L, FT_4 15.7 pmol/L and FT_3 3.7 pmol/L. Bone marrow examination revealed acute marrow aplasia with greatly reduced cellularity, increased fat spaces, markedly reduced erythropoiesis, markedly reduced granulopoiesis and reduced megakaryocytes.

Therapy with broad-spectrum antibiotics (ticarcillin/clavulnic acid and gentamicin) and daily granulocyte colony stimulating factor (G-CSF), lenograstim 263 μg/d, was commenced, as her pancytopenia progressed (Fig. 1).

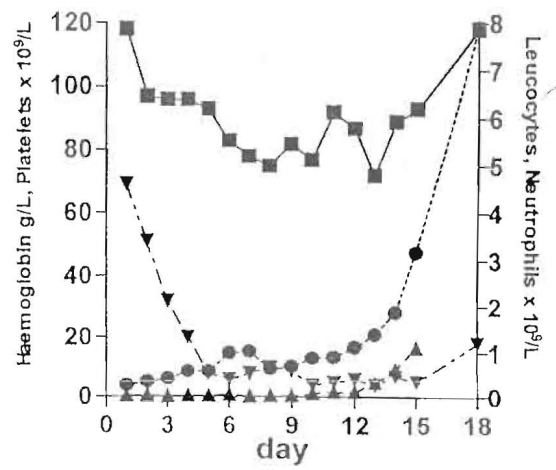

Fig. 1. Course and recovery of pancytopenia (■ Hemoglobin, ▼ Platelets, ● Leucocytes, ▲Neutrophils)

Correspondence: Duncan J Topliss, Director, Department of Endocrinology and Diabetes, Alfred Hospital, Commercial Road, Prahran, Victoria 3141, Australia.
E-mail: d.topliss@alfred.org.au

She remained febrile to 39.9°C, with negative blood and other cultures. She developed severe mucositis and required total parenteral nutrition. FT_4 was 28.6 pmol/L, FT_3 5.2 pmol/L. Lithium (250 mg qid) and cholestyramine (4gm qid, as tolerated) were recommenced. Thrombocytopenia, with platelet nadir of 8×10^9/L on day 4, was manifested by spontaneous epistaxis, gum bleeding, petechiae and vaginal bleeding. This was managed by multiple platelet transfusions and oral norethisterone therapy. Vitamin K was given orally once weekly. On day 5, 12 milliCurie (444 MBq) of ^{131}I was administered. On day 11, she developed shortness of breath with cough productive of thick sputum and blood. Chest X ray showed extensive bibasal opacification suggestive of atypical pneumonia or pulmonary hemorrhage. Anti-microbial cover, already now including vancomycin and amphotericin was broadened further with IV erythromycin.

Her neutrophils began to recover on day 11; erythrocyte recovery was evident on day 13 and platelets on day 17 (Figure 1). She was discharged on day 18. Subsequent full blood examinations have been normal. She remains euthyroid on the thyroxine replacement.

The infrequent but serious idiosyncratic drug reaction of isolated agranulocytosis (neutrophils $<0.5 \times 10^9$/L) is well recognized in 0.2-0.5% of patients on carbimazole, methimazole or propylthiouracil.[1] However, aplastic anemia is rare, with 25 cases reported in the literature, of which 13 have been adequately documented. There have been 2 fatalities from intra-cerebral hemorrhage.[2,3]

Typically, patients present with symptoms of agranulocytosis after 1-4 months of exposure to the drug. Laboratory findings of aplasia in bone marrow and pancytopenia in peripheral blood, followed by recovery of all cell lines occurred in most, with neutrophil recovery within 2-3 weeks of ceasing the drug.[3] Notably, the prognosis of carbimazole-induced aplasia appears to be better than most other forms of drug-induced aplasia, where the prognosis in linked to the degree of hypoplasia in bone marrow and peripheral blood.[2]

In this case carbimazole was ceased as soon as symptoms of neutropenia became apparent. It is probable that G-CSF contributed to granulocye recovery in this case although it has been reported that G-CSF is more effective in moderate than in severe cases of agranulocytosis.[4] To prevent recurrent hyperthyroidism, alternative treatment with lithium[1] and cholestyramine[1] proved useful prior to definitive therapy with ^{131}I. Interestingly, lithium may have an effect in promoting granulopoiesis.[5]

Routine FBE is not advocated for patients who commence thionamides. As this idiosyncratic hematologic complication generally presents rapidly in outpatient settings, it is important for clinicians to provide verbal and written instructions cautioning patients to promptly report symptoms that suggest agranulocytosis.

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