CARBIMAZOLE-INDUCED APLASTIC ANAEMIA–A CASE REPORT

Vijay AP, Lim SS, Tan ATB, Rokiah P and Chan SP
Department of Medicine (Endocrinology), Faculty of Medicine, Universiti Malaya, Kuala Lumpur

ABSTRACT

Antithyroid drugs have been used for more than 50 years for the management of hyperthyroidism. Most patients tolerate treatment well, but some may develop rare life threatening side effects such as agranulocytosis and aplastic anaemia. Clinical experience with the latter condition is extremely limited. We report on a case of carbimazole-induced aplastic anaemia caused by hypocellular bone marrow and associated plasmacytosis in a thyrotoxic patient chronically treated with carbimazole. This resolved after substitution with propylthiouracil. The clinical course was complicated by neutropaenic septicaemia and atrial fibrillation. *(JUMMEC 2009; 12 (2): 92-95)*

KEYWORDS: *thyrotoxicosis, carbimazole, aplastic anaemia, plasmacytosis*

Introduction

A 37-year old single Malay male who smoked 20 cigarettes a day, presented to us on the 9 February, 2007, with a two week history of fever, chills, sore throat, lethargy, decreased exercise tolerance, dyspnoea, vomiting, diarrhoea, loss of appetite and loss of six kilograms in weight.

He had been diagnosed with Graves' disease and thyrotoxicosis in 1996 and treated with carbimazole and propranolol by his general practitioner, but he had not been compliant and stopped treatment in December 2006. He was initially presented to another tertiary centre on 19 January, 2007, and was noted to be thyrotoxic and in atrial fibrillation. He was commenced on carbimazole 20 mg BD and propranolol 20 mg TDS and discharged. Full blood counts (FBC) at this time showed haemoglobin (Hb) 14.9 g/dL, leucocytes (WC) 6.7 x 10^9 /L and platelets (Plt) 201 x 10^9 /L. He was discharged the next day and became unwell a week later.

Methodology

On admission, he was alert and comfortable, but dehydrated, tremulous, and febrile at 38.3°C. His throat was erythematous with a small right cervical lymph node. A small diffuse goiter was present and lid lag was noted, but there were no other eye signs. He was in atrial fibrillation with an apical rate of 146/min, but reverted spontaneously to sinus rhythm of 90/min. There was no evidence of cardiac decompensation. TSH <0.01 mlu/L, free T4 95.3 pmol/L, free T3 23.2 pmol/L. Full blood count showed Hb 16.3 g/dL, WC 1.6 x 10^9 /L, ANC 0.8 x 10^9 /L, Plt 33 x 10^9 /L. Chest radiograph was normal. Carbimazole was discontinued, and he was commenced on propylthiouracil 200 mg QID, Lugol's iodine 10 drops TDS, propranolol 20 mg TDS and intravenous hydration. Antibiotic therapy with piperacillin/tazobactam 4.5 g TDS was started.

The patient's general condition improved and he was subsequently afebrile. Blood, urine and sputum cultures were negative. Platelets fell to 7 x 10^9 /L on 12 February, 2007, and he was transfused with four units of platelets although there was no bleeding tendency.

Bone marrow aspirate and trephine (BMAT) biopsy of the right posterior iliac crest on 13 February, 2007, revealed a few marrow fragments which were very hypocellular with no clumps within the stromal tissue. Lymphocytes and plasma cells were seen (Figure 1). Erythropoesis and granulopoesis were markedly depressed with dysplastic granulopoetic maturation. Megakaryocytes were virtually absent. No clusters of abnormal cells were seen and there was no increase of reticulin fibres. Granulocyte colony stimulating factor (GCSF) was not given at this stage after discussion with our haematology colleagues.

Correspondance:
Vijay Ananda A/L Paramasvaran
Department of Medicine
Faculty of Medicine, Universiti Malaya
50630 Kuala Lumpur
Email: vananda@gmail.com

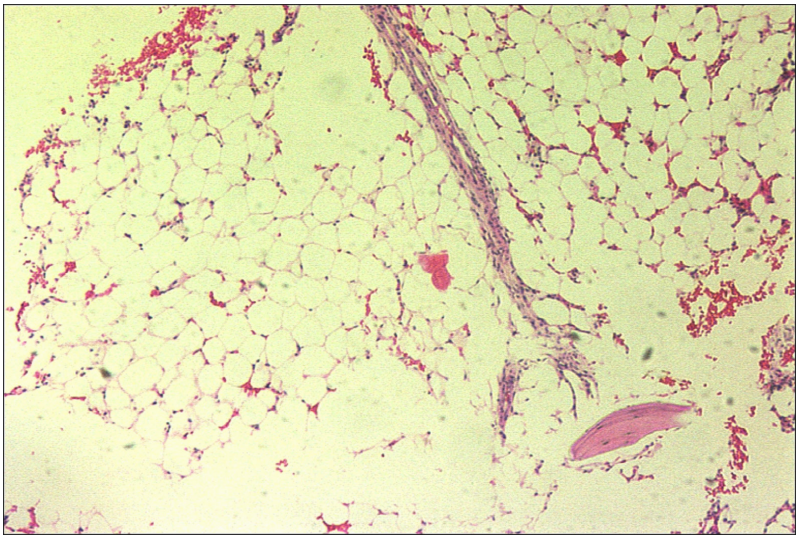

Figure 1: *Hypocellular marrow (Trephine biopsy)*

On 14 February, 2007, Lugol's Iodine was stopped. His temperature spiked to 38.2 ºC two days later, and he became hypotensive. Septic work up was repeated and his antibiotics was changed to imipenem 500 mg TDS. Propranolol was discontinued. He recovered and remained well subsequently, but had to be recommenced on propranolol on 21 February, 2007, after he was noted to be having paroxysms of atrial fibrillation. Repeat blood cultures were negative. He was discharged the same day with ciprofloxacin 500mg TDS and amoxicillin and clavulanic acid 625mg TDS. Hb was 11.8 g/dL, WC 1.6 x 10^9 /L, ANC 0.06 x 10^9 /L, Plt 20 x 10^9 109 /L.

His blood counts normalized on 12 March 2007—30 days after initial presentation (Figure 2 and 3). Transthoracic echocardiogram was normal with good left ventricular ejection fraction of 70%. He was later anticoagulated with warfarin after his platelet count had recovered. His antithyroid drugs were gradually tapered and he subsequently received radioactive Iodine 131 therapy at a dose of 10 mCi on 5 November, 2007, which rendered him euthyroid.

Discussion

The infrequent and often serious idiosyncratic drug reaction of agranulocytosis (ANC < 0.5 x 10^9 /L) is a well recognized side effect (0.2-0.5%) of treatment with the antithyroid drugs (ATD's) carbimazole, methimazole and propylthiouracil (1). However, aplastic anemia is rare with only 34 cases reported and about 17 adequately documented, not including this case. It is thought to be a humoral autoimmune response which results in transient bone marrow aplasia. Two cases have been reported with Propylthiouracil. There have been two fatalities reported from intracerebral haemorrhage (2-6).

Patients usually present with symptoms of agranulocytosis between one and four months after commencing ATD's. Unusually, in this case there is history of long term carbimazole use although this has been described in other reports (7). Laboratory findings are of aplasia of the bone marrow and pancytopaenia in the peripheral blood. Recovery of all cell lines occurred two to five weeks after discontinuing the offending drug. The prognosis with carbimazole-induced aplastic anaemia is better than with other forms of drug induced aplastic anaemia. The prognosis is linked to the degree of hypoplasia in the marrow.(2, 4).

The role of G-CSF in aiding granulocyte recovery in ATD-induced aplastic anaemia is not clear as it has been used in only three cases. Reports suggest that it may be more effective in moderate than in severe cases. No other predictors of response are known (4, 8). Due to a delay in BMAT findings, G-CSF was not given on initial presentation and was felt unnecessary later as the patient remained well clinically. Propylthiouracil was used guardedly as the patient was still markedly thyrotoxic and at risk of cardiac arrhythmias. Lithium and cholestyramine have been

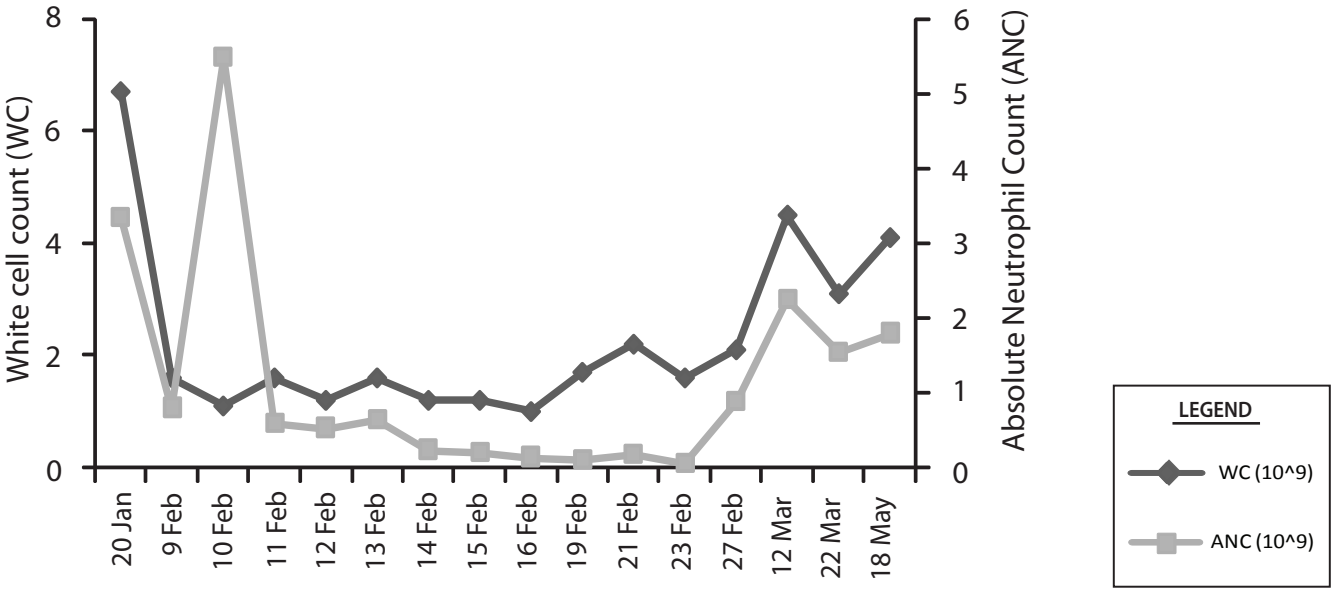

Figure 2: *Leucocyte and absolute neutrophil count trend*

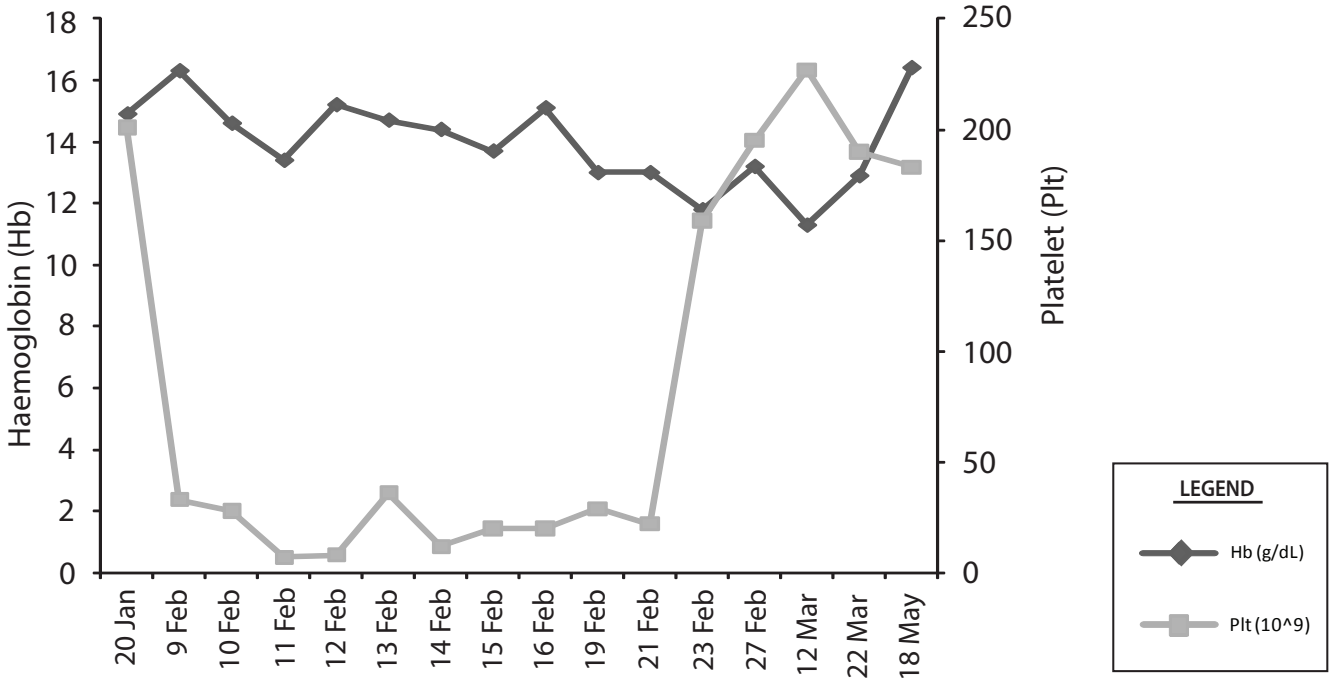

Figure 3: *Haemoglobin and platelet trend*

used to replace conventional ATD's to prevent recurrent thyrotoxicosis. Of interest, lithium may have an effect of promoting granulopoeisis (4, 8). Corticosteroids have been used successfully, but were withheld here due to the possibility of serious underlying infection (9).

To our knowledge, there are only two reports of plasmacytosis associated with carbimazole-induced aplastic anaemia. Both patients recovered after drug withdrawal with complete marrow recovery. The presence of plasma cells lends weight to an

immunogenic aetiology of this rare complication of ATD use (10, 11).

Routine FBC is not advocated in patients commencing on ATD's. It is important to provide verbal or written instructions to patients to quickly report symptoms of agranulocytosis, which predominate and can present rapidly in an outpatient setting.

References

1. Cooper DS. Treatment of thyrotoxicosis, and Wartofsky L. Thyroid storm. In: Braverman LE & Utiger RD. eds. *Werner and Ingbar's the thyroid: A fundamental and clinical text*. 8th edition. Philadelphia: JB Lippincott Williams and Wilkins; 2000: 679-684, 691-715.

2. Biswas N, You-hern A, Goldman JM, Schwartz JM. Case report: Aplastic anaemia associated with antithyroid drugs. *Am J Med Sci* 1991; 301: 190-194.

3. Escobar-Morreale HF, Bravo P, Garcia-Robles R, Garcia-Larana J, de la Calle H, Sancho JM. Methimazole-induced severe aplastic anaemia: unsuccessful treatment with recombinant human granulocyte-monocyte colony stimulating factor. *Thyroid* 1997; 7: 67-70.

4. Wilcox G, Wong R, Elliot PJ, Topliss DJ, Stockigt JR. Case report: Recovery from carbimazole-induced aplastic anaemia. *Int J of Endocrinol & Metab* 2003; 1: 41-43.

5. Moreb J, Shemesh O, Shilo S, Manor C, Hershko C. Transient methimazole-induced bone marrow aplasia: In vitro evidence for a humoral mechanism of bone marrow suppression. *Acta Haematologica* 1983; 69(2): 127-131.

6. Thomas D, Moisidis A, Tsiakalos A, Alexandrai K, Syriou V, Kaltsas G. Antithyroid drug induced aplastic anaemia. *Thyroid* 2008; 18(10): 1043-48.

7. Mezquita P, Luna V, Munoz-Torres M, Torres-Vela E, Lopez-Rodriguez F, Calleja JL, *et al*. Methimazole-induced aplastic anaemia in third exposure: successful treatment with human G-CSF. *Thyroid* 1998; 8: 791-794.

8. Gallicchio VS. Lithium stimulation of in vitro granulopoesis: evidence for mediation via sodium transport pathways. *Br J Haematol* 1986: 62: 455-466.

9. Jakucs J, Pocsay G. Successful treatment of methimazole-induced severe aplastic anaemia with recombinant human G-CSF and high dose steroids. *J Endocrinol Invest* 2006 Jan; 29(1): 74-77.

10. Brier DV, Rendo P, Gonzalez J, Shilton G, Stivel M, Goldztein S. Massive plasmacytosis due to methimazole-induced bone marrow toxicity. *Am J Haematol* 2001 Aug; 67(4): 259-261.

11. Yamamoto A, Katayama Y, Tomiyama K, Hosoai H, Hirata F, Kimura F, *et al*. Methimazole-induced aplastic anaemia caused by hypocellular bone marrow with plasmacytosis. *Thyroid* 2004 Mar; 14(3): 231-235.