Hematology

ISSN: 1024-5332 (Print) 1607-8454 (Online) Journal homepage: http://www.tandfonline.com/loi/yhem20

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To cite this article: Luana Calabrò, Andrea Alonci, Giacomo Bellomo, Arianna D'Angelo, Valeria Di Giacomo & Caterina Musolino (2001) Methimazole-Induced Agranulocytosis and Quick Recovery with G-CSF, Hematology, 5:6, 479-482, DOI: 10.1080/10245332.2001.11746546

To link to this article: https://doi.org/10.1080/10245332.2001.11746546

Published online: 13 Jul 2016.

Hematology, 2001, Vol. 5, pp. 479–482
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Infection & Marrow Failure

Methimazole-Induced Agranulocytosis and Quick Recovery with G-CSF: Case Report

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(Received 25 August 2000; In final form 20 September 2000)

A 51-year old female, treated for hyperthyroidism with methimazole, developed agranulocytosis in the third month of therapy. After discontinuing the drug, a broad spectrum antibiotic regimen plus recombinant human granulocyte colony-stimulating factor (G-CSF) were started. Her granulocyte count returned to normal with the 4° dose of G-CSF.

We think that in patients with methimazole-induced agranulocytosis, G-CSF may reduce the risk and severity of infection and in some cases should be accepted as a part of the standard therapy.

Keywords: Methimazole, agranulocytosis, G-CSF

INTRODUCTION

Evidence for cytopenia in patients treated with methimazole, because of hyperthyroidism, has been reported in literature [1].

The pathogenetic mechanism responsible of this adverse effect, sometime threatening life, is not completely clear, but the rapid hematologic recovery and the hyperplastic hematopoiesis observed in the bone marrow after drug-discontinuation suggests an immunological mechanism. Recently, targets of drug-dependent antibody on blood cells have been also identified [2].

The use of recombinant human hemopoietic colony-stimulating factor remains controversial and a broad spectrum antibiotic-therapy is, presently, standard treatment [3–11].

We report a case of a methimazole-associated agranulocytosis with quick and full recovery after discontinuation of the drug and treatment with granulocyte colony-stimulating factor (G-CSF).

CASE REPORT

A 51-year-old female was admitted to the hospital in May 2000, because of granulocytopenia and fever.

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In March 2000 Graves' disease was diagnosed and she was treated with methimazole. At that time, her blood tests were normal. After 70 days of treatment she noted the abrupt onset of fever, malaise and a sore throat. Methimazole-induced leukopenia was suspected and the drug was immediately stopped.

On admission, the temperature was 39 °C. Physical examination was normal, except for bilateral tonsillitis.

The haemoglobin was 11.2 g/dl, the platelets 220×10^9/L and the white cell count (WBC) was 1.2×10^9/L, with 98% lymphocytes and 2% eosinophiles.

Routine serum biochemistry studies showed elevated levels of C-reactive protein and erythrocyte sedimentation rate. Blood culture was positive for bacterial infection (Staphijlococcus hominis).

Antibiotic therapy was started and the fever defervesced after three days. For 10 days after stopping methimazole, the WBC count stabilised at 0.8×10^9/L. It was decided to start the patient on G-CSF at a dose of 5 μg/Kg s.c. daily. An increase of granulocyte count to $> 0.5 \times 10^9$/L was recorded on the 5th day of treatment and was preceded by an increase in the number of immature granulocyte precursors in the peripheral blood on day 4. The treatment with G-CSF was discontinued (Figure 1).

The patient was discharged home 15 days after admission to the hospital in good general condition. A follow-up one week later revealed a WBC = 4.3×10^9/L.

DISCUSSION

Agranulocytosis is an uncommon but potentially fatal complication of antithyroid drugs of the thiamide-type. The mechanism of methimazole toxicity is not fully understood, although immunological mechanisms, responsible of this adverse effects are likely involved. Recently, specific targets of drug-dependent antibody have been identified on neutrophils and erythrocites (FcγRIIIb and Rh protein respectively) [12].

G-CSF therapy has been reported to be effective for antithyroid drug therapy-induced agranulocytosis, although some patients do not

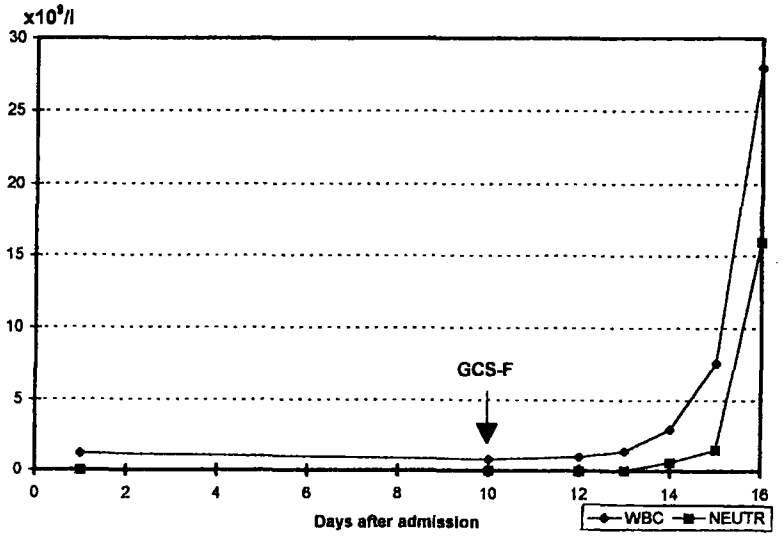

FIGURE 1 Time course of white blood cells and neutrophils count after stopping methimazole and the effect of G-CSF administration.

respond. G-CSF is one of the cytokines that increase granulocyte number, but it is still unclear its role on the drug-dependent neutropenia [13–15]. In clinical practice the haemopoietic growth factors have beneficial effects on the granulocytopenia following cytotoxic chemotherapy, or bone marrow transplantation.

Moreover, reports on autoimmune neutropenia showed that the administration of G-CSF decreased the antigranulocyte antibody (that had FcγRIIIb specifity) levels as results of an increased adsorption of antibodies by the granulocyte, or of increased plasma levels of soluble FcγRIIIb [16–21].

In our patient the hematological toxicity occured nine weeks after methimazole, which is similar to what is described in literature. This patient quickly responded to G-CSF with normalization of WBC within 16 days. This beneficial effect of G-CSF might be due in part to G-CSF's action of increasing plasma levels of soluble FcγRIIIb. Thus, we think that in some patients with methimazole-induced agranulocytosis the treatment with G-CSF is efficacious; routine use of G-CSF treatment should be further delineated by prospective studies.

Furthemore, special treatment precautions and follow-up may be required in patients treated with methimazole.

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