Thyrotoxicosis and antithyroid drugs

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A 78-year-old woman presented with fever and a sore throat for five days. Oral Augmentin (amoxicillin/clavulanate potassium) did not reduce the fever. Seven weeks prior to this episode Graves' disease had been diagnosed and treatment with methimazole 40 mg once a day and propranolol 10 mg qid was started. On admission, her temperature was 37.6°C, blood pressure was 100/70 mmHg and heart rate 76 beats/min. She had severe aphthous stomatitis with many ulcerations. The thyroid gland was palpable. Physical examination was otherwise unremarkable. Thyroid-stimulating hormone was 0.8 mU/l (normal 0.3–5.0 mU/l) and free thyroxine was 18.9 nmol/l (normal 9.5–22.4 nmol/l). A blood film (figure) was examined.

Questions

- 1 What is the diagnosis?
- 2 What is the treatment?

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Accepted 21 August 1996

Figure

Answers

QUESTION 1

The blood film shows very few white blood cells. Whole blood cell showed total leukocytes of $1.9 \times 10^9/l$ with 3.2% neutrophils and 91% lymphocytes. This is a typical picture of agranulocytosis.

QUESTION 2

Methimazole-induced agranulocytosis.

Treatment

On admission the patient was isolated. Methimazole was discontinued and treatment with mezlocillin and gentamycin was initiated along with recombinant granulocyte colony-stimulating factor (G-CSF; Neupogen filgrastim) 300 μg per day subcutaneously. She received two doses of G-CSF; 24 h after the first dose the total leucocytes count had increased to $2.1 \times 10^9/l$ with 13.2% neutrophils; 24 h following the second dose the total leukocyte count rose to $4.9 \times 10^9/l$ with 26.7% neutrophils. On the fourth day the total leucocytes were $148 \times 10^9/l$ with 53% neutrophils. The antimicrobial therapy was stopped and the patient was discharged on the fifth day.

Discussion

The patient had a typical presentation of drug-induced agranulocytosis. Patients beginning therapy with the antithyroid drugs methimazole or propylthiouracil, should be advised to notify their physician if they develop malaise, sore throat or fever persisting for more than a day or two. A complete blood count should be obtained. Drug-induced agranulocytosis may occur at any dose, irrespective of age or duration of treatment.¹ Whether routine blood counts can predict this side-effect is still debatable, but patients have developed agranulocytosis while being asymptomatic.² Once agranulocytosis has occurred the antithyroid drug is discontinued, and the patient is hospitalised and isolated in an air-filtered room. Treatment with antiseptic mouth wash and antibiotics is initiated to prevent bacterial

Learning points

- antithyroid drugs can cause agranulocytosis
- agranulocytosis can present as fever and sore throat
- once agranulocytosis is diagnosed, antithyroid drugs should be stopped and treatment with G-CSF initiated, in addition to isolation and antibiotic administration

infection. The use of steroids probably does not alter the recovery time.²

Antithyroid drugs are just some of the many drugs that can cause agranulocytosis. Granulocyte macrophage colony-stimulating factor (GM-CSF) and G-CSF are growth factors which promote the differentiation of the committed progenitor cells into mature macrophages and neutrophils. These colony-stimulating factors act on haematopoietic cells by binding to specific cell surface receptors and stimulating proliferation, differentiation and some end cell functional activation, such as phagocytosis and cytotoxicity. Endogenous G-CSF is produced when bone marrow granulocyte production is markedly inhibited.

These cytokines, G-CSF and GM-CSF, have proved useful in the treatment of neutropenia associated with severe aplastic anaemia, myelodysplastic syndrome, in patients receiving myelosuppressive chemotherapy, in patients suffering from AIDS, leukopenia,³ and in patients with cyclic neutropenia.⁴ Balkin *et al*⁵ described a patient with propylthiouracil-induced agranulocytosis, whose bone marrow had a virtual absence of myeloid elements, who responded dramatically to recombinant human G-CSF, while Tamai *et al*² reported a similar response in patients with methimazole-induced agranulocytosis. Both GM-CSF and G-CSF have been shown to be effective in the treatment of drug-induced agranulocytosis by shortening the recovery period and reducing morbidity and mortality from bacterial and fungal infections. As recombinant human GM-CSF, has dose-limited toxicity and dose limitations have not been shown for recombinant human G-CSF, the latter is recommended for the treatment of agranulocytosis induced by antithyroid drugs.²

1 Tamai H, Takaichi Y, Morita T, *et al*. Methimazole induced agranulocytosis in Japanese patients with Graves' disease. *Clin Endocrinol* 1989; 30: 525–30.

2 Tamai H, Mukuta T, Matsubayashi S, *et al*. Treatment of methimazole induced agranulocytosis using recombinant human granulocyte colony stimulating factor. *J Clin Endocrinol Metab* 1993; 77: 1356–60.

3 Bjorkholm M, Pisa P, Arver S, Beran M. Haematologic effects of granulocyte-macrophage colony stimulating factor in a patient with thiamazole induced agranulocytosis. *J Intern Med* 1992; 232: 443–5.

4 Hammond WP 4th, Price TH, Souza LM, Dale DC. Treatment of cyclic neutropenia with G-CSF. *N Engl J Med* 1989; 320: 1306–11.

5 Balkin MS, Buchholtz M. Propylthiouracil induced agranulocytosis treated with recombinant human granulocyte stimulating factor (abstract). *Proc 74th Annual Endocrine Soc*, San Antonio, TX, 1992; p 134.