

Antithyroid drug-induced agranulocytosis

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Thyrotoxicosis is a common endocrine disorder. Antithyroid drug therapy is the standard treatment for this disease, especially in young women of reproductive age. A serious side effect of antithyroid drug use, however, is agranulocytosis. We report on two patients with antithyroid drug-induced agranulocytosis. Both patients presented with fever and severe neutropenia. The administration of granulocyte colony-stimulating factor resulted in a dramatic improvement in the white blood cell count and symptoms. Antithyroid drug-induced agranulocytosis is a potentially lethal condition but is completely reversible when recognised early and when prompt treatment is offered.

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Introduction

Thyrotoxicosis is a common endocrine disorder. It affects mainly women of child-bearing age (prevalence, approximately 2%)¹ and is approximately five times more common in females than in males. Patients are usually treated with antithyroid drugs, the most common of which is carbimazole. Antithyroid drug therapy, however, is associated with a potentially fatal complication—namely, agranulocytosis. The incidence of this particular side effect has been reported to range from 0.3% to 0.6%.² Although antithyroid drug-induced agranulocytosis is rare, it has been associated with a mortality rate of 21.5%.³ We report on two thyrotoxic patients who presented with fever after having taken antithyroid drugs.

Case reports

Case 1

A 36-year-old woman with thyrotoxicosis presented to the Queen Mary Hospital (QMH) in November 1994 with a fever (temperature, 38.5°C) and a sore throat after having taken carbimazole 10 mg three times daily for 1 month. The white blood cell count at the time of the patient's hospital admission was 0.6×10^9 /L (normal range, $3.2\text{--}9.8 \times 10^9$ /L) and the neutrophil count was 0.03×10^9 /L. Intravenous imipenem was given with one dose of granulocyte colony-stimulating factor (GCSF)

300 µg subcutaneously on the day of admission. The patient's white blood cell count increased to 1.6×10^9 /L (neutrophils, 0) on day 2 and her temperature increased to 40°C. During the next few days, the white blood cell and neutrophil counts increased gradually. On day 4 of hospital admission, the white blood cell count was 4.4×10^9 /L (neutrophils, 0.68×10^9 /L) and the patient became afebrile. She was discharged home on day 7 with white blood cell and neutrophil counts of 4.1×10^9 /L and 0.80×10^9 /L, respectively, and she remained afebrile. Tests for micro-organisms gave negative results.

Case 2

A 40-year-old woman presented to the Accident and Emergency Department of the QMH in May 1998 with a fever. Thyrotoxicosis had been diagnosed 3 months previously, for which the patient had started a course of a propylthiouracil, but changed to carbimazole after 2 weeks because of gastro-intestinal disturbance. On this occasion, she was discharged home and was given oral antibiotics. She was subsequently admitted to the QMH because of persistent fever, and chest and urinary symptoms. The patient's white blood cell count at the time of hospital admission was 0.44×10^9 /L (neutrophils, 0) and her temperature was 39°C. Bone marrow examination showed normocellular marrow and a selective suppression of myelopoiesis. These symptoms were clinically compatible with a diagnosis of antithyroid drug-induced agranulocytosis. The patient was given GCSF 300 µg twice daily, followed by subcutaneous GCSF 300 µg/d and intravenous ceftazidime and amikacin. Oral itraconazole was also given on day 2 because of persistent fever. The white blood cell count increased gradually to 1.7×10^9 /L

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(neutrophils, $0.45 \times 10^9/L$) on day 3 of hospital admission and eventually increased to $11.8 \times 10^9/L$ (neutrophils, $9.80 \times 10^9/L$) on day 4, when GCSF treatment was discontinued. The patient became afebrile and tests for micro-organisms gave negative results.

Discussion

The two patients described in this report presented with antithyroid drug-induced agranulocytosis. This is a very rare complication of the use of a commonly prescribed drug. Antithyroid drug-induced agranulocytosis is diagnosed when there is a compatible clinical history, an absolute neutrophil count of $0.5 \times 10^9/L$ or less, and bone marrow histological features consistent with agranulocytosis.⁴ The diagnosis is not applicable to patients who have neutropenia due to chemotherapy, or patients with chronic neutropenia, including congenital and chronic autoimmune neutropenia.

The immune-mediated destruction of mature neutrophils was the first mechanism to be identified as a cause of antithyroid drug-induced agranulocytosis.⁴ Sprikkelman et al⁴ have described four different immunological mechanisms that may be responsible. Firstly, antibodies may develop against the antithyroid drug when it is bound to the cell membrane of the granulocyte, resulting in an accelerated destruction of the granulocyte. Secondly, antibodies may target the drug/metabolite complex that has been adsorbed to the neutrophil granulocyte in the presence of plasma component. Thirdly, the drug may trigger the production of auto-antibodies. Finally, the interaction of a granulocyte antigen and drug may induce the production of antibodies. Besides these mechanisms, idiosyncratic drug-induced agranulocytosis, which is a severe selective depression of myelopoiesis due to an unpredictable adverse reaction to a wide variety of drugs in hypersensitive individuals, has also been a postulated mechanism for agranulocytosis, as was documented for the second patient of this case report.

Drug-induced agranulocytosis usually occurs within 1 to 2 months of taking the antithyroid drug, but the onset of the disease can also be delayed, as was the case for the second patient. It has been reported that the white blood cell count usually spontaneously returns to normal over a period of 1 to 2 weeks after discontinuing treatment with the offending drug; the time taken ranges from 7 to 56 days.^{1,5} The speed of neutrophil recovery depends on the number of myeloid precursor cells that are present in the bone marrow. Recovery may be prolonged if there

is granulocyte precursor aplasia. Previous reports have suggested that giving GCSF can hasten the marrow recovery to approximately 1 week.^{1,5} This suggestion was confirmed in the two patients presented here; both patients' white blood cell count returned to within the normal range by day 4 of GCSF treatment. At the QMH, treatment is arbitrarily discontinued when the absolute neutrophil count is $1.0 \times 10^9/L$ or higher, since the optimal duration of GCSF therapy for agranulocytosis is currently unknown. Only a single dose of GCSF was used in the first patient. In contrast, GCSF treatment was stopped when the neutrophil count was higher than $0.5 \times 10^9/L$ in the second patient. The initial dose of GCSF used in the second patient was double that used in the first patient. The usual recommended dosage of GCSF is $5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$, although there is no large randomised controlled trial that compares effects of giving other dosages.

Agranulocytosis had a poor prognosis in the past, with a reported mortality rate of 21.5%.³ The mortality rate has decreased significantly in the past two decades because of the availability of potent antibiotics. The prognosis depends on a variety of factors, such as age, co-morbidity, immediate antibiotic treatment, and duration of severe granulocytopenia. Successful treatment of antithyroid drug-induced agranulocytosis by GCSF has been reported in the literature.^{1,6} A mortality rate of 5% has been reported for 58 patients with severe agranulocytosis who were treated with GCSF.⁴ These data indicate that GCSF enhances the recovery of the peripheral blood granulocytic lineage, which results in a faster normalisation of the peripheral blood granulocyte count, as well as a reduced incidence of fatal complications. This treatment has been recommended for most circumstances, and GCSF has been purified, molecularly cloned, and expressed as a recombinant protein.⁷ It is a potent stimulus for normal neutrophil proliferation and maturation *in vitro* and *in vivo*. Other approved indications include idiopathic aplastic anaemia, idiopathic neutropenia, and chemotherapy-associated agranulocytosis.

Antithyroid drug-induced agranulocytosis is diagnosed at the QMH by paying careful attention to the drug history of patients who present with fever. Not all patients with agranulocytosis have fever or other symptoms of infection, however, and some patients can be totally asymptomatic. Tajiri et al⁷ have suggested that continuing antithyroid drug treatment in patients with asymptomatic agranulocytosis might actually cause permanent damage to the marrow. This suggestion raises the important issue of regularly monitoring the white blood cell count in patients who are taking antithyroid drugs.⁷

Asawa et al⁸ have recommended that the leukocyte differential count be checked, as patients with a normal white blood cell count may have a low neutrophil count.⁸ The practical difficulty, however, is that thyrotoxicosis is a very common disease and hence many patients take antithyroid drugs. In addition, the white blood cell count can be falsely reassuring if normal, or unnecessarily worrisome if relatively low. It is therefore more practical and more cost-effective for doctors to instruct patients who are taking antithyroid drugs to have their white blood cell count checked if they have a fever or sore throat, rather than to have routine regular monitoring.⁹ Doctors should also have a high index of suspicion of agranulocytosis when they encounter such patients.

References

1. Tavintharan S, Rajasoorya C, Chew LS. Carbimazole-induced agranulocytosis—a report of 2 recent cases. *Singapore Med J* 1997;38:386-7.
2. Genet P, Pulik U, Lionnet F, Bremont C. Use of colony-stimulating factors for the treatment of carbimazole-induced agranulocytosis [letter]. *Am J Hematol* 1994;47:334-5.
3. Julia A, Olona M, Bueno J, et al. Drug-induced agranulocytosis: prognostic factors in a series of 168 episodes. *Br J Haematol* 1991;79:366-72.
4. Sprikkelman A, de Wolf JT, Vellenga E. The application of hematopoietic growth factors in drug-induced agranulocytosis: a review of 70 Cases. *Leukemia* 1994;8:2031-6.
5. Ng SC. Carbimazole-induced agranulocytosis treated with granulocyte-macrophage colony stimulating factor—a case report. *Ann Acad Med Singapore* 1995;24:465-6.
6. Gerl A, Gerhartz H, Wilmanns W. GM-CSF for agranulocytosis [letter]. *J Intern Med* 1991;230:90-1.
7. Tajiri J, Noguchi S, Okamura S, et al. Granulocyte colony-stimulating factor treatment of antithyroid drug-induced granulocytopenia. *Arch Intern Med* 1993;153:509-14.
8. Asawa T, Arai M, Takeda T, Aizawa T, Yamada T, Onishi Y. Antithyroid drug-induced agranulocytosis: is routine white blood cell count effective for the detection [letter]? *Arch Intern Med* 1992;204-7.
9. Sobel R, Glick S. Monitoring antithyroid therapy [letter]. *Arch Intern Med* 1993;153:2797.