Antithyroid drug–induced agranulocytosis

CH Lee, RHS Liang

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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Key words: Agranulocytosis; Antithyroid agents; Granulocyte colony-stimulating factor

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 0.6x10^9 /L (normal range, 3.2-9.8 x 10^9 /L) and the neutrophil count was 0.03x10^9 /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 1.6x10^9 /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 4.4x10^9 /L (neutrophils, 0.68x10^9 /L) and the patient became afebrile. She was discharged home on day 7 with white blood cell and neutrophil counts of 4.1x10^9 /L and 0.80x10^9 /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 0.44x10^9 /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 1.7x10^9 /L

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immune neutropenia. Neutropenia, including congenital and chronic auto-
penia due to chemotherapy, or patients with chronic disease is not applicable to patients who have neutro-
phils, 0.45x10^9/L on day 3 of hospital admission and eventually increased to 11.8x10^9/L (neutro-
phils, 9.80x10^9/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 agranulo-

Agranulocytosis had a poor prognosis in the past, with a reported mortality rate of 21.5%.

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 spontaneous 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.

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. 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 1.0x10^9/L or higher, since the optimal duration of GCSF therapy for agranulo-
cytosis 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 0.5x10^9/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 µg·kg^{-1}·d^{-1}, although there is no large randomised controlled trial that compares effects of giving other dosages.

Antithyroid drug–induced agranulocytosis is diag-

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 pa-
tients with agranulocytosis have fever or other symptoms of infection, however, and some patients can be totally asymptomatic. Tajiri et al have suggested that continuing antithyroid drug treatment in patients with asymptom-
tomatic agranulocytosis might actually cause permanent damage to the marrow. This suggestion raises the impor-
tant issue of regularly monitoring the white blood cell count in patients who are taking antithyroid drugs.

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Lee et al have recommended that the leukocyte differential count be checked, as patients with a normal white blood cell count may have a low neutrophil count. 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. Doctors should also have a high index of suspicion of agranulocytosis when they encounter such patients.

References