

**CASE REPORT**

# A case of antithyroid drug-induced agranulocytosis from a second antithyroid drugs (ATD) administration in a relapsed Graves' disease patient who was tolerant to the first ATD treatment

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**Key Clinical Message**

Agranulocytosis is a rare side effect of antithyroid drugs (ATD) that usually develops within the first 3–6 months after starting treatment. We present a 64-year-old patient who developed agranulocytosis after starting ATD to treat relapsed Graves' disease. This patient had tolerated the first course of ATD for 72 months. This was an unusual case in which a serious side effect developed during a second ATD course. It is essential that clinicians remain vigilant to the fact that antithyroid drugs can induce agranulocytosis several years after initiated.

**KEYWORDS**

agranulocytosis, antithyroid drug, Graves' disease

## 1 | INTRODUCTION

Graves' disease (GD) is an autoimmune disorder that produces antibodies to the thyroid-stimulating hormone (TSH) receptor.<sup>1</sup> Management of GD, as suggested by the American Thyroid Association, includes antithyroid drugs (ATD), <sup>131</sup>I therapy, and thyroidectomy.<sup>2</sup> Methimazole (MZ) and carbimazole (CZ), antithyroid medications that inhibit thyroid peroxidase, are currently the first drugs of choice for medical management of GD in adults. MZ and CZ are associated with adverse side effects, mostly occurring within the first 3 months of initiating therapy.<sup>3</sup> Agranulocytosis is a rare but fatal side effect of ATD with incidence reported at 0.1%–1%.<sup>4</sup> Here, we present a 64-year-old female patient with relapsed GD who developed severe agranulocytosis after 3 weeks on CZ treatment. Although this patient had previously undergone successful GD treatment with MZ for 72 months, agranulocytosis occurred after 3 weeks of CZ administration for relapsed GD.

## 2 | CASE PRESENTATION

A 64-year-old female patient was referred to our clinic with relapsed GD. This patient initially presented at age 57 years with palpitation, sweating, and weight loss for 1 month. She was diagnosed with GD and started MZ at an initial dose of 30 mg/day and a beta-blocker for symptom management, prescribed by an endocrinologist from an outside hospital. She tolerated MZ and continued this therapy on a gradually reducing dose. Finally, she discontinued MZ after 6 years, when she was 63 years old. Medical records denied any prior clinical evidence of agranulocytosis, such as unexplained fever or sore throat, during the period, she was taking MZ. At discontinuation of MZ treatment, her thyroid function test was optimally controlled, but TSH receptor antibody (TSH-R Ab) was slightly higher (11.03 IU/L, normal if <1.5 IU/L).

Five months after discontinuing ATD, overt hyperthyroidism was observed with an elevated free T4 level of 4.54 ng/mL (0.82–1.76 ng/dL), T3 level of 3.28 ng/mL (0.6–1.81 ng/

mL), and suppressed TSH at  $<0.01$  uIU/mL (0.55–4.78 uIU/mL). TSH-R Ab was elevated at 12.49 IU/L, but TSI bioassay (normal range  $<140\%$ ) was normal (37%). Initial absolute neutrophil count (ANC) was normal, but aspartate transaminase and alanine transaminase were slightly elevated. The patient started CZ at 10 mg/day with a beta-blocker for symptom relief. After 3 weeks on this treatment dose, the patient reported 2 days of sore throat and intermittent fever. She reported no sick contacts, travel history, or taking other medications. Physical examination revealed tachycardia, mild fever ( $38.6^{\circ}\text{C}$ ), and bilateral submandibular lymph node enlargement. Blood tests revealed ANC of 0 cells/ $\mu\text{L}$ . Other tests, including blood, urine, and throat cultures, were within normal limits. Blood chemistry, including a liver function test, was normal. CZ-induced agranulocytosis was strongly suspected based on negative findings for other causes. Fever subsided after the second day of administration.

Based on a strong suspicion of ATD-induced agranulocytosis, CZ was immediately halted. Broad spectrum antibiotics were administered, and granulocyte colony-stimulating factor (G-CSF) was injected subcutaneously. ANC remained at 0 cells/ $\mu\text{L}$  for the first 4 days despite administering 300 mcg/day G-CSF. ANC increased to 20 cell/ $\mu\text{L}$  over the next 2 days and then decreased to 0 cell/ $\mu\text{L}$  on days seven and eight, after which it increased. Follow-up testing after 14 days off CZ showed ANC at 2250 cell/ $\mu\text{L}$ . G-CSF was stopped at day 14. For the management of hyperthyroidism, we administered 27 g/day of cholestyramine, KI solution 5 mL t.i.d., and a beta-blocker while ATD was stopped. The patient was discharged on day 16 without development of any further complications. At discharge, her ANC was 1790 cell/ $\mu\text{L}$ . One month after development of agranulocytosis, ANC had recovered to within the normal range. After recovery, she was administered  $^{131}\text{I}$  radioiodine for definitive treatment of GD.

### 3 | DISCUSSION

MZ and CZ are the standard therapies for GD. Both drugs inhibit the enzyme thyroperoxidase, which acts in thyroid hormone synthesis. CZ is a precursor of MZ and is widely used in Korea. CZ is rapidly converted to MZ in serum. MZ and CZ have identical mechanism of action and are considered identical.<sup>2</sup> Propylthiouracil (PTU) was used for treating GD until serious reports of its hepatotoxic effects were published. PTU is the third most common cause of drug-induced liver transplant in the United States.<sup>5</sup> Adverse effects are also associated with the use of MZ/CZ. From minor side effects (pruritus and urticaria) to major adverse effects (agranulocytosis and even Stevens-Johnson syndrome), diverse spectrum of side effects has been reported.<sup>6</sup> Agranulocytosis is defined as a granulocyte count  $<500$  cell/ $\mu\text{L}$ .<sup>7</sup> It is a rare occurrence, with an

incidence from 0.2% to 0.5%,<sup>8</sup> and is usually observed within 3 months after starting ATD.<sup>9,10</sup> Various reports have investigated the timing of the development of agranulocytosis after initiation of MZ/CZ therapy. In Japan, Nakamura et al<sup>10</sup> retrospectively reviewed 854 cases of agranulocytosis following use of ATD and found that more than 70% of patients who developed this side effect did so within 2 months, and that nearly 85% did so within 3 months. Only 15.4% of patients developed agranulocytosis after more than 4 months and only one patient developed the condition 15 months after ATD use.<sup>10</sup> In pediatric patients, 4% of children develop ATD-induced agranulocytosis much later, even beyond 18 months.<sup>11</sup> More recently, Puthenpura et al<sup>12</sup> reported a case of a six-year-old patient who developed agranulocytosis 18 months after initiation of MZ therapy. In addition, the MZ/CZ dose contributes to agranulocytosis. Patients receiving MZ at 30–60 mg/d showed an agranulocytosis rate of 1%,<sup>13</sup> which rose to 8% at 120 mg/d.<sup>14</sup>

The mechanism of ATD-induced agranulocytosis is unclear. Recently, Hirotohi et al suggested two possible mechanisms: (1) an immune-mediated process and (2) direct intoxication.<sup>10</sup> Guffy et al<sup>15</sup> reported the presence of complement-dependent IgM antibodies against granulocytes in a patient receiving PTU. Regarding the direct intoxication process, Wall et al<sup>16</sup> demonstrated the existence of circulating antibodies to differentiated granulocytes, monocytes, and myeloid and erythroid progenitor cells. Generally, agranulocytosis caused by immune-mediated processes proceed rapidly, whereas destruction of granulocytes by direct intoxication occurs after a few weeks.<sup>10</sup>

In the present case, we observed agranulocytosis 3 weeks after initiation of CZ at 10 mg/d, in a patient who had previously been tolerant of MZ for 72 months. As Guffy et al<sup>15</sup> suggested, immunogenic abnormalities that underlie drug sensitivities and induce direct intoxication may be genetic, and some patients may be more susceptible, as in the present case. The most important lesson from this case is that clinicians must remain vigilant for agranulocytosis from antithyroid drugs regardless of treatment duration or dose.

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### AUTHOR CONTRIBUTION

HK, JL, JH: were participated in patient management and data collection, contributed to the interpretation of the case, and critically reviewed the manuscript. All authors: approved the final manuscript as submitted.

## CONFLICT OF INTEREST

The authors have declared that no conflict of interest exists.

## INFORMED CONSENT

Written informed consent was obtained from the patient to publish this case report.

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