Sudden Onset Agranulocytosis and Hepatotoxicity after Taking Methimazole

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Abstract

Agranulocytosis is a rare adverse effect of methimazole. The usual duration of treatment prior to the onset of agranulocytosis is approximately 1 to 4 months, and can be as long as 1 year. Agranulocytosis together with hepatotoxicity is an extremely rare idiosyncratic side effect of methimazole treatment. We present an unprecedented case of a Grave’s disease patient who showed a strong reaction to methimazole with obvious agranulocytosis and hepatotoxicity which developed only six days after administration. This case, along with a literature review, is offered with the aim to increase the awareness of physicians of sudden onset agranulocytosis and hepatotoxicity from methimazole.

Key words: agranulocytosis, hepatotoxicity, methimazole, hyperthyroidism


Introduction

Thyrotoxicosis refers to any condition characterized by an excess of circulating thyroid hormones leading to multisystem involvement. Antithyroid drugs (ATDs), especially methimazole (MMI), are commonly prescribed in China to control hyperthyroidism because they are effective, cheap and convenient in a once-daily dose (1). MMI does cause some side effects; the most frequent reaction is rash and pruritus seen in 3-5% of patients (2). The fatal side effects of MMI include agranulocytosis, hepatotoxicity, aplastic anemia and vasculitis (3). Agranulocytosis, which is the most feared among these complications, occurs in 0.35 percent of patients receiving MMI. Most cases of agranulocytosis occur within the first 2-3 months of therapy initiation (3, 4). Hepatotoxicity, which is another adverse reaction of thionamides, usually appears in the first few weeks of treatment, with an incidence of 0.1-0.2% (3, 5). In very few cases (6, 7), these two situations can happen on the same patient. Here, a case of agranulocytosis and hepatotoxicity induced by MMI is presented; the duration of MMI therapy before the onset of serious complications was only six days.

Case Report

A 38-year-old woman visited a local hospital with complaints of weight loss, palpitations, sweating and irregular menstrual cycle. She was diagnosed with hyperthyroidism. At that time, her blood count and liver function test were within the normal range. She then started treatment with MMI (20 mg once daily) and propranolol (10 mg thrice daily). Six days after taking these drugs, she had a sore throat without any other infection symptoms such as fever, cough or diarrhea. She went to a community hospital and had a routine blood test. Her full blood count showed total WBCs 0.33×10⁹/L with neutrophils 0.03×10⁹/L and lymphocytes 0.29×10⁹/L, platelets 269×10⁹/L and hemoglobin 104 g/L. She was recommended to suspend MMI immediately and was transferred to our hospital the following day.

On admission, her blood pressure was 105/70 mmHg, pulse rate 115/min, respiratory rate 22/min and body temperature 38°C. Her glance was brisk with mild ophthalmopathy. Her skin was warm, moist and hand tremors were observed. She had a diffuse goiter and slightly enlarged tonsils. Liver and spleen were not palpable below the costal margin. She had no prior history with regard to hematologi-
She was admitted to a single ward with barrier nursing and isolation precautions. Further examination results were as follows: Thyroid function tests revealed free T3 8.75 pg/mL (2.3-4.2 pg/mL), free T4 4.18 ng/dL (0.89-1.76 ng/dL), and thyroid-stimulating hormone (TSH) 0.02 μIU/mL (0.35-5.50 μIU/mL). Thyroidal I-131 uptake rate was 83% at 3 hours (10-15%) and 79% at 24 hours (25-62%). Liver function tests showed total bilirubin 26.4 μmol/L (6-20.5 μmol/L), direct bilirubin 10.7 μmol/L (0-7.8 μmol/L), AST 166 IU/L (5-40 IU/L), ALT 226 IU/L (10-42 IU/L) and ALP 143 IU/L (30-290 IU/L). Perinuclear antineutrophil cytoplasm antibodies (p-ANCA) and cytoplasmic antineutrophil cytoplasmic antibodies (c-ANCA) were not detected in her serum. Viral hepatitis A, B, C and E and other hepadnavirus such as Epstein-Barr virus, Cytomegalovirus, Varicella zoster virus, and Simple herpes virus were excluded. Serum protein turbidimetry revealed polyclonal hypergamma globulinemia with elevated IgG levels 24.23 g/L (8-18 g/L) and IgE 2.87 g/L (0.1-1.0 g/L). Blood culture was performed prior to the use of antibiotics, and it yielded negative results. Bone marrow aspiration showed hyperplasia with normal erythropoiesis and megakaryocyte proliferation, but the granulocyte precursors were markedly reduced. The ratio of granulocyte-to-erythrocyte count (G:E) was 0.16 (Figure). Ultrasonograph showed diffuse goiter and normal liver. ECG indicated sinus tachycardia. Initial chest X-ray showed no abnormalities, but three days later the second inspection revealed lower left lung infection. Based on these data, we reached a diagnosis of acute agranulocytosis and hepatotoxicity attributed to the use of MMI, secondary pulmonary infection in a Graves disease patient.

On admission to our hospital, we began using intravenous antibiotics (Piperacillin & tazobactam) to control infection and hepatoprotective drug (Reduced glutathione) to lower transaminase. Granulocyte-colony stimulating factor (G-CSF) was prescribed to raise neutrophils with an initial dose of 100 μg/day. Due to poor response and sustained agranulocytosis, the dosage was increased to 300 μg/day on the 6th day. Neutrophil count was increased to 2.64×10^7/L on the 11th day, then the fever was subsided and liver function recovered to normal range (shown in Table). The patient was discharged on the 15th day and received I-131 treatment on the same day. Her absolute neutrophil count and transaminase remained at normal levels and symptoms of hyperthyroidism were improved in the subsequent months.

**Discussion**

ATD-induced agranulocytosis tends to occur within 2 or 3 months after starting treatment, some cases were even reported to develop after several months or after 1-2 years of MMI treatment (8). However, sudden onset agranulocytosis cases, especially those complicated with other fatal side effects, are rare. To our knowledge, this is the first case of agranulocytosis along with hepatotoxicity onset within six days in a Graves disease patient who was treated with methimazole.

To date, pathogenic mechanisms of these adverse reactions can not be fully explained. There are two major explanations of agranulocytosis, including direct toxic effects and immunological reactions (3). ATD can readily penetrate the marrow affecting oxygen and glucose utilization of leukocytes through the oxidized metabolites (9). Toxic effects require 20 to 40 days of exposure, and the onset is insidious. It is dose and concentration dependent (10). There have been several studies suggesting that MMI-induced agranulocytosis is dose related (8, 11, 12), but in the present patient, this theory seems unreasonable, because this patient developed agranulocytosis only six days after commencement of MMI (total dosage 120 mg), which is a much shorter time than other patients reported (8, 13, 14). Also the concentration of MMI in the present case should be in a low level. In addition, bone marrow examination is useful in revealing the characteristics of direct toxic effects in agranulocytosis. Hypoplasia with decreased or absent precursor cells is a common characteristic of drug toxic effects of bone marrow (15, 16). In the present patient, the bone marrow showed hyperplasia with normal erythroid and lymphoid progenitor cells, only granulocyte precursors were signifi-
cantly reduced. Therefore, her bone marrow function was not suppressed. These results indicated that the agranulocytosis of the patient may not be caused by direct toxic effects.

As for the immunological mechanisms, a study reported that serum obtained from a patient during MMI-induced agranulocytosis inhibited in vitro the myeloid progenitor cells growth from autologous and allogeneic bone marrow (17). This data suggests an immune-mediated mechanism rather than direct toxic effects of the drug, but the precise mechanisms have not been clarified (3, 18). Several studies have reported that antineutrophil cytoplasm antibodies (ANCA) might contribute to propylthiouracil- (PTU) induced agranulocytosis but these have not been observed in MMI therapy (18, 19). The present patient was taking MMI with ANCA negative in serum. Therefore, these explanations cannot illuminate the pathogenesis of this patient. Other immunological reactions include immunoglobulin E-mediated hypersensitivity reaction, drug-induced immunoglobulin G and M responses, and neutrophil-drug complex (14, 20). Coincidentally, the serum levels of IgE and IgG were elevated in this case. Perhaps these immune mechanisms may play a role in the onset of the process.

Hepatotoxicity is another serious reaction to antithyroid drugs. The estimated incidence of antithyroid drug-associated hepatotoxicity ranges from 0.1% to 0.2%, although the true incidence is unknown (3, 6). Fulminant liver function failure associated with thiouamides can be fatal in 25-50% of cases (21). PTU-induced liver dysfunction is more common than MMI-induced liver dysfunction (22). MMI-associated hepatic abnormalities are typical of cholestatic process (23). The mechanisms of hepatotoxicity for the two antithyroid drugs have not been clarified in detail. Immune injury may also act as an important role in the process (3, 6). In the present case, the clinical features fulfilled the diagnostic criteria of drug-induced hepatotoxicity (24). In relation to the current illness, viral hepatitis infection was excluded by serological determinations and there was no history of chronic liver disease, alcohol abuse, or drug use. The characteristics of her liver damage were similar to allergy-related hepatitis, with a significant elevation in transaminase instead of bilirubin and onset abruptly after the exposure to MMI. Fortunately, her liver dysfunction was mild to moderate, not severe compared with the cases reported to date (22, 23, 25), and the hepatotoxicity improved dramatically after MMI was suspended and hepatoprotective treatment was administered. All of the information discussed above indicate that the acute immune response may be the cross pathogenesis of agranulocytosis and hepatotoxicity for this case.

MMI induced agranulocytosis and hepatotoxicity are dangerous because they may occur unexpectedly and may be complicated by life threatening sepsis or liver function failure. To detect them timely is particularly important. Clinical evidence is usually the abrupt onset with fatigue, sore throat, anorexia or fever as common presenting complaints, but some patients may not have any symptoms in the early phase (15). The present patient was identified for throat discomfort without any other infection symptoms. Therefore, conducting a routine blood cell count with liver function test and educating patients about the common symptoms of agranulocytosis and hepatotoxicity may contribute to an early diagnosis.

### Conclusion

This is the first case of agranulocytosis and hepatotoxicity induced by methimazole in less than six days. This particular case suggests that methimazole might cause agranulocytosis and liver dysfunction via acute immune-mediated mechanisms in a very short period of time. Physicians should be alert and evaluate the blood neutrophil count and liver biochemistry in clinically suspect cases.

The authors state that they have no Conflict of Interest (COI).

### References

1. He CT, Hsieh AT, Pei D, et al. Comparison of single daily dose of methimazole and propylthiouracil in the treatment of Graves’ hy-


