CASE REPORT

ONLINE EXCLUSIVE

THE PATIENT
51-year-old woman

SIGNS & SYMPTOMS
– History of Graves disease
– General fatigue, palpitations, and hand tremors

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The authors reported no potential conflict of interest relevant to this article.

doi: 10.12788/jfp.0690

THE CASE
A 51-year-old Japanese woman presented with fever, sore throat, and dyspnea of less than 1 day's duration. Although she had developed general fatigue, palpitations, and tremors of the hands 2 months earlier, she had not sought medical care.

Her medical history included Graves disease, which had been diagnosed 13 years earlier. She reported that her only medication was methimazole 10 mg/d. She did not have any family history of endocrinopathies or hematologic diseases.

Physical examination revealed a body temperature of 99.7 °F; heart rate, 130 beats/min; blood pressure, 182/62 mm Hg; respiratory rate, 46 breaths/min; and oxygen saturation, 100% on room air. Pharyngeal erythema was seen. Lung sounds were clear. The patient had tremors in her hands, tenderness of the thyroid gland, and exophthalmos. No leg edema or jugular vein distension was seen.

Laboratory tests indicated hyperthyroidism, with a thyroid-stimulating hormone level < 0.01 μIU/mL (normal range, 0.5-5 μIU/mL); free T3 level, 4.87 pg/mL (normal range, 2.3-4.3 pg/mL); and free T4 level, 2.97 ng/dL (normal range, 0.9-1.7 ng/dL). The patient also had a white blood cell (WBC) count of 1020 cells/μL (normal range, 3500-9000 cells/μL) and neutrophil count of 5 cells/μL (normal range, 1500-6500 cells/μL).

Other blood cell counts were normal, and a chest x-ray did not reveal any abnormal findings. In addition, there was no evidence to suggest hematologic malignancies or congenital neutropenia.

THE DIAGNOSIS
Based on the patient's low WBC and neutrophil counts, agranulocytosis due to antithyroid drug therapy was suspected; however, this diagnosis would be highly unusual in the context of a 13-year history of therapy. Further history taking revealed that, because of her lack of financial means, unstable living conditions, and lack of understanding of the necessity for medication adherence, the patient had not taken methimazole regularly until 2 months prior to presentation, when she started taking it because of worsening symptoms. She had hesitated to report her social and medication status due to embarrassment.

In consideration of these factors, a diagnosis of exacerbation of hyperthyroidism and agranulocytosis (due to methimazole restart and upper respiratory infection) was made.

DISCUSSION
Agranulocytosis is a severe adverse event of antithyroid agents and requires prompt diagnosis and treatment. In a 26-year study at one clinic, it occurred in approximately 0.4% of patients taking antithyroid agents.[1] The possible mechanisms of agranulocytosis are the direct toxicity of drugs and immune-mediated responses.[2] Older age, female sex, and some HLA

genotypes are reported to be associated with susceptibility to agranulocytosis.[2]

Although the development of agranulocytosis tends to be dose related, a small dose of antithyroid agent can sometimes cause the condition.[3,4] It usually occurs within the first 3 months of treatment initiation, but occasionally patients develop agranulocytosis after long-term therapy.[5] Interruption and subsequent resumption of the same antithyroid drug treatment also can be a risk factor for agranulocytosis, as in this case.[5]

Treatment includes drug cessation, administration of broad-spectrum antibiotics if infection is suspected, and granulocyte-colony stimulating factor (G-CSF) therapy.[5]

Our patient was hospitalized, and methimazole was stopped immediately. Administration of potassium iodide 50 mg/d and G-CSF was started. Meropenem 3 g/d also was administered for neutropenic fever.

The patient's condition improved, and her WBC count increased to 1640 cells/μL on Day 8 and 10,890 cells/μL on Day 9. G-CSF was stopped on Day 12 and meropenem on Day 13. Bone marrow aspiration was not performed because of improvement in lab values and her overall condition. Although monitoring of WBC count during methimazole therapy is controversial,[5] we decided to routinely monitor this patient due to the possibility of drug cross-reactivity.

Despite repeated explanations that it was dangerous for a patient who had developed agranulocytosis to take another antithyroid medication, the patient refused surgical treatment or radioiodine ablation because of her financial situation. (While all Japanese citizens are covered by a national health insurance program, patients ages 6 to 70 years are required to pay approximately 30% of medical and pharmaceutical costs.) On Day 21, potassium iodide was stopped, and propylthiouracil 300 mg/d was administered with careful follow-up. Agranulocytosis did not recur.

Immediate problem solved, but what about the future?

During her hospital stay, the medical team spoke with the patient many times, during which she expressed anxiety about her health conditions and the difficulties that she had experienced in her life. The clinicians acknowledged her concerns and assured the patient of their continuing commitment to her well-being even after discharge. The patient also was advised that she should take her medication as prescribed and that if she had a fever or sore throat, she should stop the medication and seek medical care as soon as possible. The patient accepted the medical team's advice and expressed hope for the future.

Conversations about medication adherence. In 1 survey, about 60% of patients taking antithyroid drugs were unfamiliar with the symptoms of agranulocytosis.[6] To deliver safe and effective treatment and detect conditions such as agranulocytosis at an early stage, clinicians must communicate clearly with patients who have hyperthyroidism, providing sufficient explanation and ensuring understanding on the patient's part.

Patients may be reluctant to provide the details of medication adherence.[7] Although it is common for patients to need services for socioeconomic issues,[8] health care professionals sometimes fail to adequately discuss these issues with patients, especially if the patients are marginalized and/or have lower economic status.[9] Cases such as ours underscore the importance of improving clinicians' awareness and sensitivity to patients' socioeconomic challenges.[10,11]

Our patient received information about welfare and other government services from a medical social worker during her hospital stay. She also was informed that she could seek assistance from medical social workers in the future if needed.

The patient was discharged on Day 28. After discharge, she took propylthiouracil as prescribed (300 mg/d), and her Graves disease was well controlled. Outpatient follow-up visits were performed every 1 or 2 months. No adverse events of propylthiouracil were seen in the ensuing time.

THE TAKEAWAY

Patients with chronic conditions sometimes discontinue medications, and they may not talk about it with their medical team, especial-

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ly if they have socioeconomic or other difficulties in their lives. Clinicians should consider medication nonadherence and its risk factors when patients with chronic conditions develop unexpected adverse events. JFP

ACKNOWLEDGMENT

We thank Jane Charbonneau, DVM, from Edanz for doing an English-language review of a draft of this manuscript.

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