The onset of antineutrophil cytoplasmic antibody-associated vasculitis immediately after methimazole was switched to propylthiouracil in a woman with Graves’ disease who wished to become pregnant

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Abstract. Propylthiouracil (PTU) is recommended as a first-line antithyroid drug (ATD) during first trimester organogenesis in pregnancy because recent evidence suggests that methimazole (MMI) may be associated with congenital anomalies. However, PTU more commonly causes myeloperoxidase (MPO)-antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, which usually occurs during prolonged treatment, compared with MMI. We report a case of MPO-ANCA-associated vasculitis in a 35-year-old woman with Graves’ disease. Although her thyroid function could be maintained euthyroid by MMI, her ATD was switched to PTU because she wished to become pregnant. The patient presented with flu-like symptoms 8 days after starting PTU and developed hemoptysis and dyspnea at 22 days. Her MPO-ANCA titer was 21 ELISA units (EUs) before PTU treatment but increased to 259 EUs at 22 days after PTU treatment. Her clinical condition improved with the discontinuation of PTU and with immunosuppressive therapy. This case indicated that MPO-ANCA vasculitis occurred within several weeks after the initiation of PTU and that this side effect could be caused by the change from MMI to PTU. Thus, our clinical observation suggests that patients treated with PTU should be carefully monitored for MPO-ANCA titers and variable manifestations of MPO-ANCA-associated vasculitis regardless of the period of administration.

Key words: Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, Methimazole, Propylthiouracil, Graves’ disease, Pregnancy
and are likely to receive PTU might increase.

Patients with myeloperoxidase (MPO)-anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis present with variable manifestations, such as fever, skin involvement, myalgia, arthralgia, scleritis, glomerulonephritis and pulmonary hemorrhage, and most cases have high MPO-ANCA titers [7]. The development of MPO-ANCA-associated vasculitis has recently been documented in Graves’ disease patients treated with ATDs [8-13]. Although the clinical characteristics and the pathogenesis of MPO-ANCA-associated vasculitis are still unclear, these severe side effects are more commonly observed with PTU than MMI [11]. Additionally, this adverse reaction can usually occur during prolonged treatment [14] and may be more frequent when the drug is resumed than when it is first given [15].

We describe a rare case of MPO-ANCA-associated vasculitis that occurred within several weeks after MMI discontinuation and subsequent PTU administration in a woman with Graves’ disease who planned to become pregnant.

Case Report

A 35-year-old woman was diagnosed with Graves’ disease at another hospital 18 years prior to her current presentation. Treatment with PTU was initiated at the time of diagnosis. Three years after her diagnosis, PTU was changed to MMI because it was difficult to manage. Three years after the initiation of MMI, her Graves’ disease was in remission, and MMI was discontinued in 1998. However, she experienced a relapse in 2000, and treatment with MMI was restarted at her request. Her thyroid function was maintained as euthyroid by MMI treatment without side effects. In April 2010, 10 mg of MMI daily was switched to 150 mg of PTU daily at the other hospital because she wished to become pregnant. Eight days later, the patient presented with flu-like symptoms, including fever (37.5°C), headache and cough. She was admitted to our hospital because she developed hemoptysis, dyspnea and congestion of the eyes 22 days after the initiation of PTU therapy. The patient had no history of illness, except for Graves’ disease. She smoked approximately 10 cigarettes/day, did not drink alcohol and had no allergies. There was no family history of notable illness, including autoimmune disease.

On physical examination at admission, the patient’s temperature was 37.9°C; pulse, 120 beats/min; blood pressure, 120/68 mmHg; and respiratory rate, 30 breaths/min. Her palpebral conjunctiva was slightly anemic, and her bulbar conjunctiva was congested. Her temporal artery was not tender. The patient had no exophthalmos, and her thyroid gland was not palpable. There was no jugular venous distention. Her carotid pulses were normal and without bruits. There were diffuse inspiratory fine lung crackles, without wheeze. Cardiac examination revealed a normal S1 sound and a physiologically split S2 sound, without a murmur, rub or gallop. The abdomen was not tender, there were no masses, and hepatosplenomegaly and bruits were not present. There was no rash, ulcer, peripheral edema, subcutaneous nodule, lymphadenopathy or musculoskeletal tenderness. Neurologic examination was normal. The patient received a score of 15 out of 15 points on the Glasgow Coma Scale.

The leukocyte count was 3500 /μL with a normal differential. The hemoglobin and platelet counts were 8.9 g/dL and 16.0×10⁴ /μL, respectively. Her serum parameters were the following: blood urea nitrogen level, 12 mg/dL [reference range, 8-20 mg/dL]; creatinine, 0.55 mg/dL [reference range, 0.5-1.1 mg/dL]; albumin, 2.5 g/dL [reference range, 3.9-4.8 g/dL]; and creatine kinase, 6 U/L [reference range, 40-190 U/L]. The levels of electrolytes and liver transaminase were normal. The level of C-reactive protein (CRP) was 11.45 mg/dL [reference value, <0.3 mg/dL]. Urinalysis showed mild proteinuria and glomerular hematuria, and she was negative for erythrocyte casts. Her arterial blood gases were pH 7.42, PCO₂ 37.9 mmHg and PO₂ 81.8 mmHg with the patient breathing oxygen at 10 L/min through a face mask. Her serum thyroid parameters were as follows: thyroid-stimulating hormone (TSH) level, 0.003 μIU/mL [reference range, 0.27-4.2 μIU/mL]; free thyroxine (fT4), 2.00 ng/dL [reference range, 1.1-1.8 ng/dL]; and free triiodothyronine (fT3), 5.30 pg/mL [reference range, 2.6-5.1 pg/mL]. Her anti-nuclear antibody and anti-glomerular basement membrane (GBM) antibody results were negative. A Gram stain of the sputum was negative.

An electrocardiogram showed sinus tachycardia. A chest radiograph revealed extensive, diffuse bilateral alveolar infiltrates (Fig. 1). Computed tomography (CT) of the chest showed multifocal areas of consolidations with air bronchograms in both lung fields (Fig. 2). Ultrasonography of the abdomen was unremarkable. Transthoracic echocardiography demonstrated...
normal biventricular size and function, and there were no valvular abnormalities.

Immediately after admission, PTU was discontinued because of presumed PTU-induced vasculitis. Additionally, 2 g ceftriaxone (CTRX) intravenously every 24 h and 400 mg ciprofloxacin (CPFX) intravenously every 12 h were started because the possibility of bacterial infection could not be completely excluded. We planned to start treatment with prednisolone and inorganic iodine and discontinue PTU because of the possibility of PTU-induced ANCA-associated vasculitis accompanied by organ involvement, including the lung and kidney, and the hyperthyroid state [10]. However, the patient refused the use of these drugs. To confirm the diagnosis of vasculitis, bronchoscopy, surgical lung biopsy and renal biopsy were considered. However, they were not performed because the patient developed severe refractory hypoxemia on admission, and her urinalysis returned to normal within a few days after the cessation of PTU.

After 7 days in the hospital, the patient’s MPO-ANCA titer at admission was reported to be 259 ELISA units (EUs) [reference range, 0-20 EUs]. A blood sample collected 3 months before the initiation of PTU treatment showed a titer of 21 EUs when it was reanalyzed 2 days after hospitalization. Multiple blood cultures and sputum cultures were all negative after 7 days of hospitalization. Therefore, the patient’s disorder was diagnosed as PTU-induced MPO-ANCA-associated vasculitis, and 30 mg of prednisolone daily (0.6 mg/kg/day) was started. CTRX and CPFX were stopped, and 40 mg per day of inorganic iodine was started.

After the withdrawal of PTU and the initiation of immunosuppressive therapy, the patient’s symptoms including fever, hemoptysis, dyspnea and eye congestion gradually improved, which was accompanied by the normalization of laboratory findings, as shown in Fig. 3. On hospital day 23, prednisolone was tapered to 25 mg daily and the patient was discharged.

The patient’s treatment was continued at the other hospital. Immunosuppressive therapy with prednisolone was slowly tapered for 3 months and discontinued in August 2010. The patient underwent radioactive iodine ablation as a definitive therapy for Graves’ disease in June 2010. The MPO-ANCA titer gradu-
however, similar cases may occur in proportion to the prevalence of these guidelines. Therefore, our rare case suggests that physicians must consider the possibility of the onset of MPO-ANCA-associated vasculitis with PTU, particularly in regard to the recent recommendation for the management of ATD therapy associated with pregnancy.

MPO-ANCA-associated vasculitis usually occurs during prolonged PTU treatment [14], but there have been several cases occurring within a few months after beginning treatment [11]. Recently, Noh et al. investigated the clinical characteristics of MPO-ANCA-associated vasculitis caused by ATDs with a large number of adverse side effect reports from a Japanese pharmaceutical company that markets ATDs [11]. Their study demonstrated that the median time of onset was 42 months (range, 1-372 months) after beginning drug therapy.

ally decreased to 138 EUs in June 2010, 43 EUs in November 2010 and 21 EUs in January 2012.

**Discussion**

The side effects of ATDs occur more frequently with PTU than with MMI [4]. Thus, it is accepted that PTU should not be used as a first-line ATD [16]. Nevertheless, PTU is recommended as a first-line ATD in the first trimester of pregnancy [5, 6]. In fact, our patient changed her ATD based on recommendations for PTU use during pregnancy, although her thyroid function had been previously maintained as euthyroid with MMI. Unfortunately, she developed MPO-ANCA-associated vasculitis immediately after the initiation of PTU. No similar case report has previously been observed in women hoping to become pregnant; however, similar cases may occur in proportion to the prevalence of these guidelines. Therefore, our rare case suggests that physicians must consider the possibility of the onset of MPO-ANCA-associated vasculitis with PTU, particularly in regard to the recent recommendation for the management of ATD therapy associated with pregnancy.
treatment. Moreover, our patient developed MPO-ANCA-associated vasculitis within several weeks of the initiation of PTU. It is not possible to predict when this side effect might occur, but the immediate discontinuation of ATDs has led to good prognoses in some cases [10, 13, 17]. In contrast, serious complications have been reported when ATDs have been continued because of unawareness of this adverse reaction [18, 19]. In these regards, our clinical observation also suggests that patients treated with PTU should be carefully monitored for MPO-ANCA titers and variable manifestations of MPO-ANCA-associated vasculitis, such as fever, skin involvement, myalgia, arthralgia, scleritis, glomerulonephritis and pulmonary hemorrhage, regardless of the period of administration. We must be particularly careful of a urinalysis finding because crescentic glomerulonephritis may be confirmed even if it is only a mildly abnormal result [20].

An important question remaining why our patient developed MPO-ANCA-associated vasculitis in an extremely short period after the initiation of PTU compared with other cases showing a similar clinical course [10, 11]. A previous case with viral infection suggested the so-called ANCA cytokine sequence theory [13]. Our patient also presented with flu-like symptoms 8 days after starting PTU. However, we could not distinguish between the symptoms of a viral infection and manifestations of MPO-ANCA-associated vasculitis. Finally, we consider the switch from MMI to PTU itself to be another cause of the unique clinical presentation in our patient due to the cross-reaction between PTU and MMI and the side effects of ATD therapy [8].

The slight increase in the MPO-ANCA titer induced by PTU or MMI may have been involved in the severe vasculitis. These results suggest that switching from MMI to PTU could be equal to the resumption of PTU, which is well known to induce MPO-ANCA-associated vasculitis more frequently than the initiation of PTU [15]. Thus, clinicians should be vigilant about the induction of MPO-ANCA-associated vasculitis, particularly when PTU is initiated following MMI.

In summary, we described a rare case of MPO-ANCA-associated vasculitis that occurred immediately after switching from treatment with MMI to PTU in a woman with Graves’ disease who wished to become pregnant. Based on the Japanese guidelines for the therapy of Grave’s disease [5], the number of women with Graves’ disease in Japan who wish to become pregnant and are likely to receive PTU may increase. Our case report suggests that patients treated with PTU should be carefully monitored for MPO-ANCA titers and variable manifestations of MPO-ANCA-associated vasculitis regardless of the period of administration. In particular, if there is a history of use of PTU or MMI, it is recommended that the MPO-ANCA titers be measured before using PTU. The immediate discontinuation of PTU should be considered if MPO-ANCA-positive sera or these manifestations are confirmed.

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References

appearance of antineutrophil cytoplasmic antibodies in some patients with Graves’ disease. *Thyroid* 10: 595-599.


