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Image of Interest

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Propylthiouracil-Induced Antineutrophil Cytoplasmic Antibody-Positive Vasculitis and Agranulocytosis: A Rare Case with Life-Threatening Multiple Systemic Manifestations

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Propylthiouracil (PTU) has been used to manage hyperthyroidism; however, various PTU-induced adverse effects, including severe illnesses, such as hepatic failure, cholestatic jaundice, splenomegaly, lupus-like syndrome, agranulocytosis, and antineutrophil cytoplasmic antibody (ANCA)-positive vasculitis have been described [1]. PTU has been implicated in inducing ANCA-associated vasculitis, and agranulocytosis involving neutrophil destruction is known to be associated with immune-mediated induction of ANCA antibodies after PTU medication [2,3]. However, the exact ANCA induction pathogenesis and progression to vasculitis or agranulocytosis in patients receiving PTU medications remains to be elucidated. Most patients with PTU-associated ANCA-positive vasculitis have good outcomes with less severe renal involvement than those with idiopathic vasculitis, and withdrawal of PTU usually results in disease resolution [2]. Acute respiratory distress syndrome with alveolar hemorrhage is uncommon presentation of the PTU [4]. Here, we report a rare case of a patient with life-threatening PTU-induced ANCA-positive vasculitis involving subcutaneous and pulmonary vessels and agranulocytosis.

A 65-year-old female patient with complaints of general weakness and multiple skin lesions was admitted to our endocrinology clinic. She was diagnosed with hyperthyroidism 10 years ago, underwent PTU treatment for 2 years, and maintained remission. There were no drug history and suspicious clinical suspicious findings of other autoimmune disease. Three days before presentation, she complained of a skin lesion that occurred after repeating PTU treatment at a private clinic due to weight loss, sweating, and palpitations that had occurred 2 months ago. At the time of presentation to our clinic, she had been taking PTU 50 mg daily for 1 month with stable thyroid disease. No family history of vasculitis or other autoimmune diseases; however, on examination, she had a low-grade fever of 37.6°C and mildly-diffused enlarged non-tender goiter with no evidence of thyroid eye disease. She had mild lower limb edema and large numbers of vasculitic skin lesions on the arms, chest, bilateral lower extremities, and abdomen (Fig. 1A). Initial investigations showed a neutrophil count of 800/μL, white cell count of 2,200/μL, and normal hemoglobin and platelet counts. Renal and liver functions were normal; thyroid function was subclinical hyperthyroidism with thyroid stimulating hormone 0.02 mIU/L (reference range, 0.25 to 4.0 μIU/mL; Cisbio Bioassays, Bedford, MA, USA) and free thyroxine 1.22 ng/dL (reference range, 0.7 to 1.9; Immunotech, Blainville, QC, Canada).

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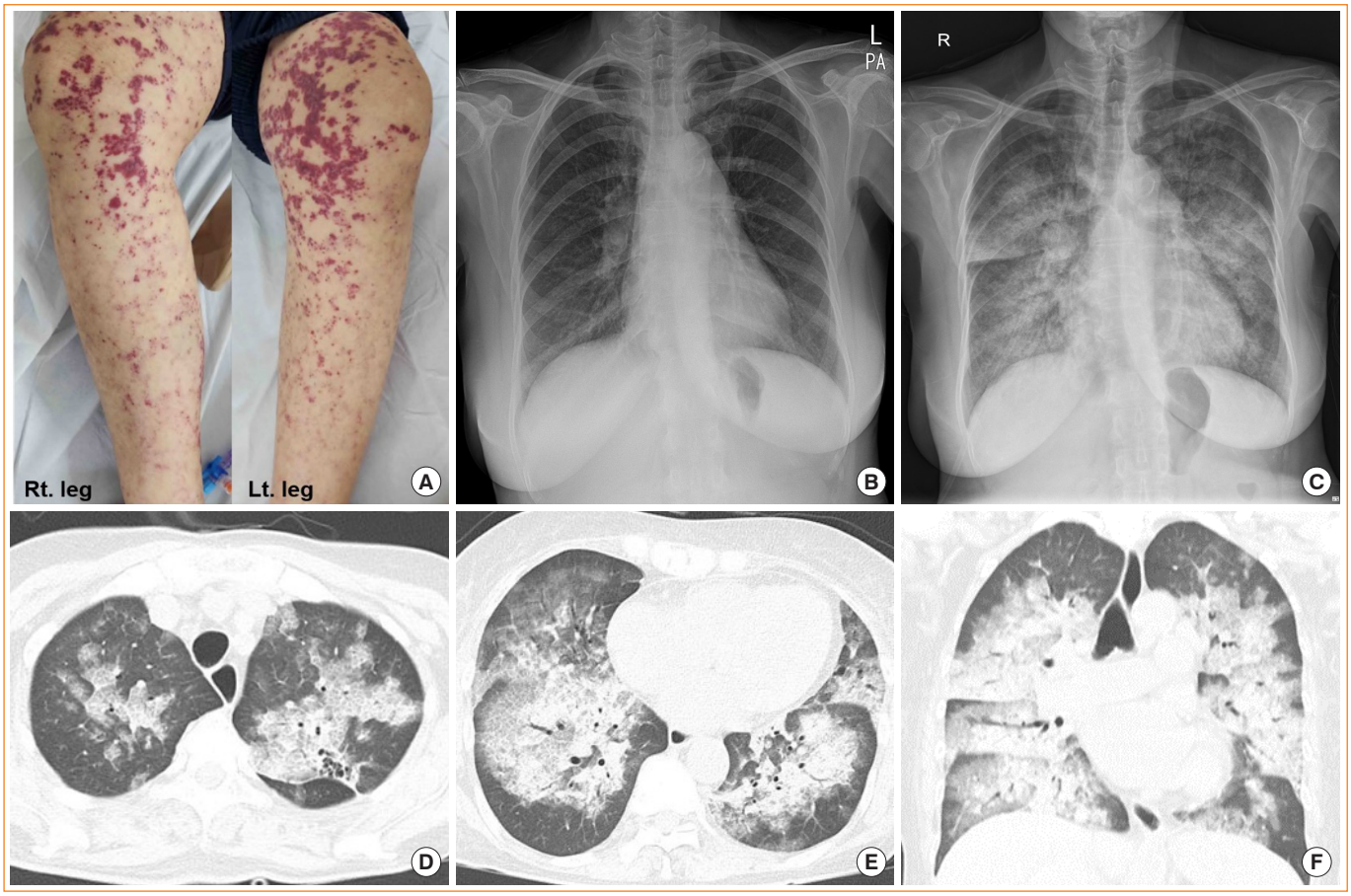

Fig. 1. The representative images of the patient. (A) Representative images of skin lesion showed that blanching erythematous skin lesions are present on her bilateral lower extremities. (B) Initial chest X-ray at admission was normal. (C) Chest X-ray at the time the patient's symptoms worsened showed diffuse haziness in both lung fields. (D, E, F) Representative coronal or sagittal images of chest computed tomography revealed diffuse acinar opacities, ground-glass opacity, and septal thickening in both lungs.

Blood and urine cultures were repeatedly negative, and extended viral screen was also negative. Routine blood chemistry and complete urinalysis were normal, hepatitis markers were negative, and both the cytoplasmic-ANCA and perinuclear-ANCA tests were positive. Chest radiography was normal (Fig. 1B), and vital signs were stable. There was no evidence of active infection, and we suspected PTU-induced agranulocytosis and ANCA-associated vasculitis. PTU treatment was discontinued, and close observation with empirical antibiotics and one dose of granulocyte colony-stimulation factor (G-CSF) was performed. We consulted a rheumatologist and decided to monitor vasculitis without using an immunosuppressive agent while neutropenia improved. The neutrophil count and white cell count were within the normal range 12 hours after admission, and the skin lesions had no significant change. The patient suddenly developed acute hypoxia and tachypnea 20 hours after admission, which initially manifested as a vocal cord clot, causing hoarseness. Chest X-ray showed diffuse haziness in both lung fields (Fig. 1C). Diffuse acinar opacities, ground-glass opacity, and septal thickening were observed in both lungs on chest computed tomography (Fig. 1D-F). The appearance was primarily interpreted as a massive alveolar hemorrhage. The patient received intravenous methylprednisolone (methylPD) pulse therapy (1 g). She developed worsening hypoxic respiratory failure (pH 7.25, PaO_2 54.8 mm Hg, $PaCO_2$ 56 mm Hg), was intubated, transferred to the intensive care unit, and mechanically ventilated. During tracheal intubation, the patient had massive hemoptysis at 2 L per day, continued red blood cell transfusion and methylPD pulse therapy; however, hypoxemia despite ventilator care was continued, and the patient died on hospital day 4.

This is a rare case of a patient who experienced concomitant agranulocytosis and ANCA-associated vasculitis as an adverse

effect of PTU treatment for Graves' disease. Agranulocytosis refers to a reduction in the absolute neutrophil count to less than 500 cells/μL, which renders the patient susceptible to infection [5]. Antithryoid drug-related agranulocytosis is a potentially life-threatening complication observed in 0.2% to 0.5% of patients with Graves' disease [5]. In our case, agranulocytosis recovered after one G-CSF administration, and since there was no evidence of infection on physical examination and several labs, it was probably not a life-threatening reason. Moreover, most ANCA-associated vasculitis due to PTU resolves completely upon discontinuation of the drug, precluding the need for immunosuppressive therapy [1]. Our case is rare, in which a patient with agranulocytosis and vasculitis confined to a skin lesion developed a very sudden diffuse alveolar hemorrhage within 24 hours and died. In this case, the mechanism of agranulocytosis and vasculitis co-occurrence caused by antithyroid drugs is unclear. However, it suggests that continuous attention is required for the risk of sudden exacerbation of vasculitis due to an adverse immune reaction.

We obtained consent from the patient for submission of the thesis on this case (IRB 2023-01-066).

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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