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Propylthiouracil-Induced Vasculitis With Alveolar Hemorrhage Confirmed by Clinical, Laboratory, Computed Tomography, and Bronchoscopy Findings: A Case Report and Literature Review

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Abstract

Introduction: Propylthiouracil (PTU) is commonly used to treat hyperthyroidism and can induce antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis. Although this is a rare side effect, ANCA-associated vasculitis can progress to severe disease if its diagnosis and treatment are delayed, leading to a poor prognosis.

Case Presentation: A 43-year-old woman with Graves' disease developed pulmonary vasculitis and diffuse alveolar hemorrhage (DAH) associated with ANCA against myeloperoxidase and proteinase-3 that was confirmed by computed tomography (CT) and bronchoscopy and treated with PTU. The symptoms and signs of alveolar hemorrhage were rapidly resolved after PTU withdrawal and treatment with corticosteroids. After 6 months of follow-up, the patient maintained complete ANCA-negative clinical remission status, as confirmed by normal CT and bronchoscopy findings. To our knowledge, this is the first documented case of bronchoscopic comparison of PTU-induced DAH before and after steroid treatment.

Conclusions: Patients treated with PTU should be closely monitored and followed up, even if the drug has been used for several years. When patients develop progressive dyspnea with alveolar opacities on chest imaging that cannot be explained otherwise, alveolar hemorrhage should be an important differential diagnosis while investigating the case. Early diagnosis and prompt discontinuation of the PTU treatment are essential for improving patient outcomes.

Keywords: Vasculitis, Antineutrophil Cytoplasmic Antibody (ANCA), Thyroid Disease, Graves' Disease

1. Introduction

Propylthiouracil (PTU), one of the most commonly used antithyroid drugs, was introduced for clinical use in 1947 for the treatment of Graves' disease (GD). PTU can cause a variety of adverse effects, including skin rashes, pancytopenia, hepatic impairment, lupus-like syndrome, and vasculitis (1-3). PTU-induced vasculitis can involve many organs, including the cutaneous, musculoskeletal, respiratory, gastrointestinal, hematological, renal, and neurological systems (1-6).

PTU is known to induce antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) as a rare side effect (7, 8). ANCA is an important serological marker of systemic vasculitis and known to be associated with drug-induced vasculitis (7, 8). Three staining patterns are known: perinuclear (p-ANCA), cytoplasmic (c-ANCA), and atypical. Stankus and Johnson (7) reported the first case of ANCA-positive vasculitis in 1992 in a patient with GD under PTU treatment. In 1993, Dolman et al. (8) described the detection of ANCA in the serum of six patients who developed vasculitis during PTU treatment for hyperthyroidism. Thereafter, many similar cases complicated with AAV have been reported in patients with GD, most of whom were taking PTU. Although patients with this condition almost always tested positive for myeloperoxidase (MPO) or p-ANCA, not all patients who developed ANCA while on thionamides had clinical symptoms (9). Physicians need to remain vigilant for PTU-induced vasculitis because the onset of this condition varies widely from 1 week to 10 years (10).

Here we present and discuss the case of a patient with GD who developed diffuse alveolar hemorrhage (DAH) secondary to PTU-induced AAV and experienced complete remission after stopping PTU and starting treatment with a corticosteroid. This rare but intriguing case highlights the importance of including AAV in the differential diagnosis of alveolar hemorrhage symptoms and immediately stopping PTU treatment and starting corticosteroid treatment.

2. Case Presentation

A 43-year-old Chinese Han woman with a history of GD was referred to our department for recurrent cough, expectoration for 2 months, and hemoptysis accompanied by fever for 1 week. Physical examination of the neck showed a slightly enlarged and homogenous thyroid gland, and a bilateral lung examination by auscultation was unremarkable. Her medical history was significant only for GD, which had developed 5 years previously and was treated with PTU. She had no history of other cardiovascular or cerebrovascular risk factors; allergic diseases including asthma, allergic rhinitis, or urticarial; and psychosocial disorders and no family history of autoimmune diseases. PTU was initially started at 300 mg/day and decreased to 100 mg/day once the euthyroid status was obtained.

In the fourth year of treatment, the patient started nonsteroidal anti-inflammatory drug (NSAID) treatment for arthralgia. In the fifth year of treatment, she developed recurrent cough and expectoration accompanied by malaise and asthenia but denied any experience of a rash, weight loss, or myalgia. After 2 months of ineffective treatment with antibiotics, the patient developed hemoptysis and fever, with a peak temperature of 37.9°C. Chest CT showed diffuse alveolar infiltrates, and pneumonia was considered. Moxifloxacin was then added to treat the bacterial infection. Two weeks later, however, the patient still had fever, cough, and hemoptysis. Repeat CT scan showed much more severe lesions with diffuse, bilateral, predominantly lower lobe nodular infiltrates and ground-glass opacity (Figure 1A). A diffuse segmental hemorrhage was noted on bronchoscopy with a needlepoint hemorrhage and partial fusion in the submembrane along the left main bronchus spreading to the opening of the left upper lobe (Figure 2A).

Examination of the bronchial lavage fluid revealed 98% macrophages with iron staining positive for siderophages, and negative culture findings. Laboratory examinations revealed normal free triiodothyronine (2.18 pg/mL, normal range [NR] = 2 - 4.4), free thyroxine (0.98 ng/dL, NR = 0.93 - 1.7), and thyroid stimulating hormone (1.05 uIU/mL, NR = 0.27 - 4.2); low thyroglobulin (0.5 ng/mL, NR = 1.4 - 7.8); significantly elevated thyroglobulin antibody

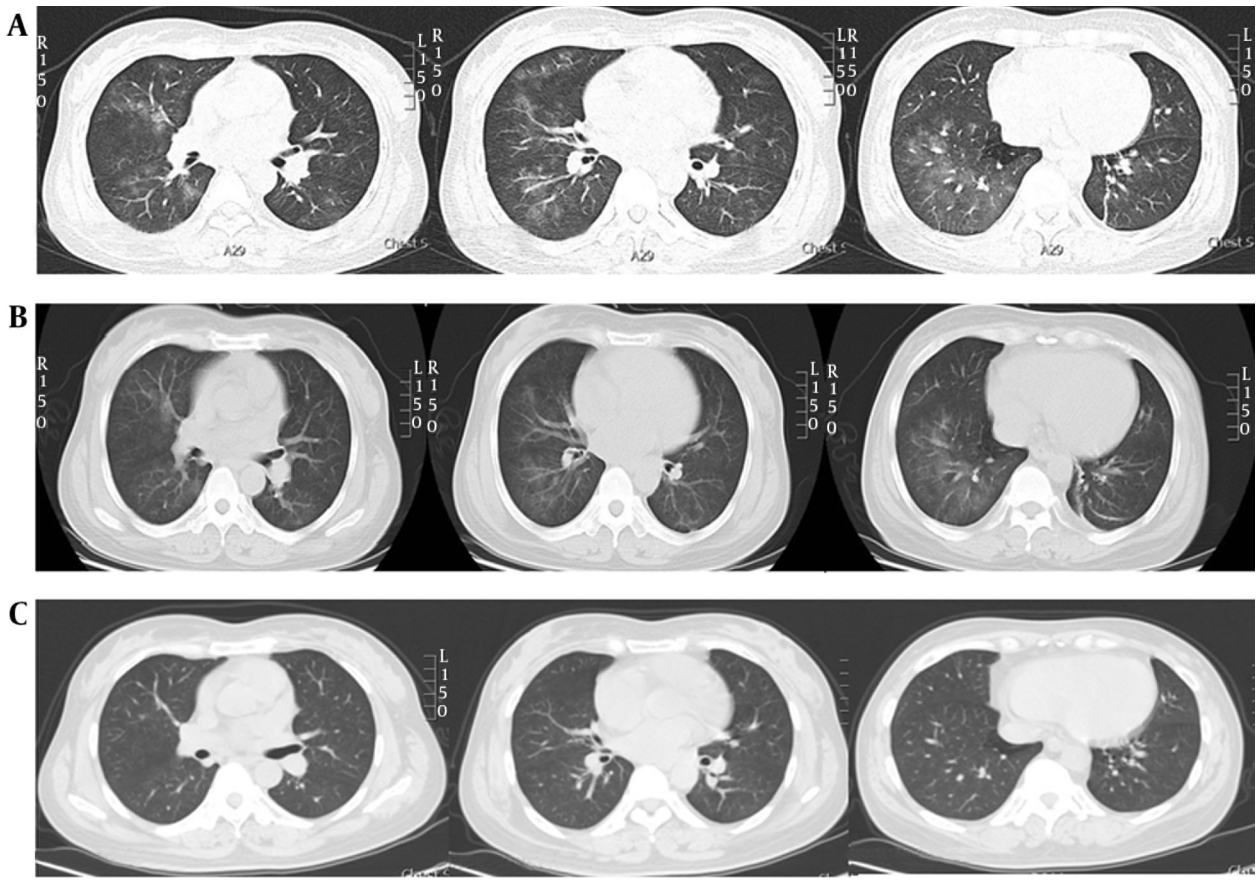

Figure 1. A, High-resolution chest computed tomography performed at admission, revealing diffuse bilateral alveolar infiltrates and ground-glass opacification, predominantly in the middle and lower lung fields, consistent with pulmonary hemorrhage; B, after 2 weeks of PTU withdrawal and steroid treatment, high-resolution chest computed tomography showed improvement in alveolar infiltrates and ground-glass opacity; C, after 6 weeks of PTU withdrawal and steroid treatment, high-resolution chest computed tomography showed restoration of the lung parenchyma, with the alveolar infiltrates and ground-glass opacity completely disappeared.

(> 4000 IU/mL, NR = 0 - 115) and antithyroid peroxidase antibody (256.4 IU/mL, NR = 0 - 34); gradually increased erythrocyte sedimentation rate (ESR; 80 - 112 mm/h, NR = 0 - 20); and slightly increased C-reactive protein (CRP; 39 mg/L, NR = 0 - 8). Enzyme-linked immunosorbent assays were positive for MPO-ANCA and proteinase 3 (PR3)-ANCA, while immunofluorescent assays were positive for p-ANCA and c-ANCA. The complete blood cell count indicated slight anemia, with a decrease in hemoglobin (HGB) from 123 g/L to 89 g/L (NR = 113 - 151). Coagulation study revealed a slightly elevated D-dimer (1.11 mg/L, NR < 0.55).

Liver and kidney functions were normal. Antinuclear antibody, anti-extractable nuclear antigen, and anti-double-stranded DNA were not detected. Pulmonary function test items were normal. Abdominal ultrasonography and cerebral magnetic resonance imaging were unremarkable. Thyroid ultrasonography disclosed a diffusely enlarged thyroid gland with hypervascularity indicative of GD. Based on these findings, this patient was diagnosed with PTU-induced ANCA-positive pulmonary vasculitis with DAH. The PTU was discontinued promptly, and an intravenous injection of methylprednisolone (80 mg/day) was initiated. Three days later, the steroid dose was changed to 40 mg/day. One week later, the therapy was changed to oral prednisolone, which was then tapered over next 12 weeks. There was significant improvement in respiratory symptoms and fever 1 week after the start of prednisolone treatment and PTU withdrawal. Within days, antithyroid antibody titers and ESR decreased markedly.

Approximately 1 month after our observation, the serum was tested negative for ANCA, and ESR and HGB level were normal. In addition, chest CT indicated restoration of the lungs; it showed rapid improvement in the pulmonary pathology (Figure 1B) with an almost complete recovery in the parenchyma (Figure 1C) that was subsequently confirmed with bronchoscopy (Figure 2B). After 6 months of follow-up, the patient was asymptomatic at 3 months of follow-up with a negative ANCA. Whole blood and thyroid function tests revealed normal ESR, CRP, and D-dimer levels. The steroid dose was tapered. At the 6-month follow-up, steroids were discontinued, and the ANCA remained negative. The patient's condition remains stable.

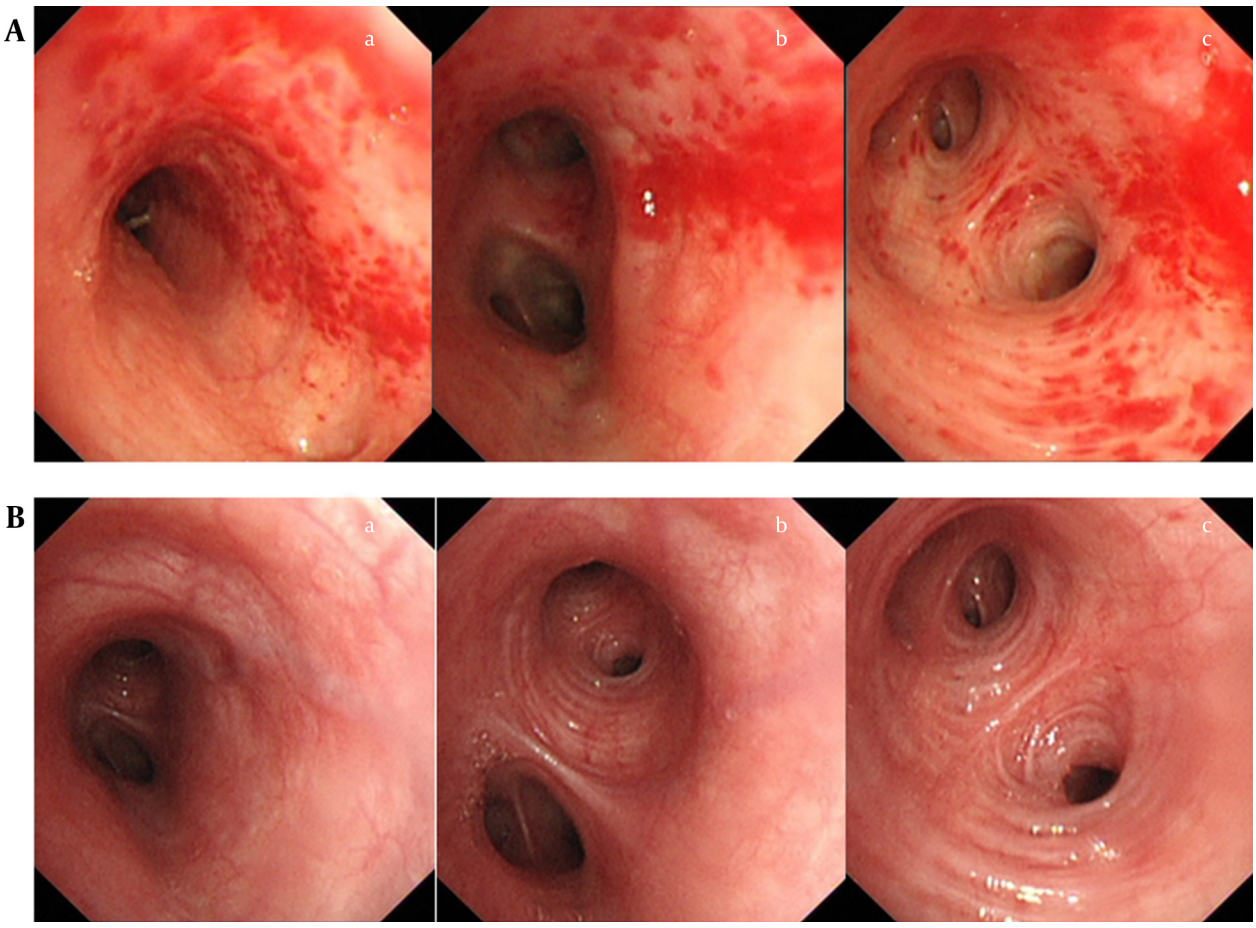

Figure 2. A, bronchoscopic image showing needlepoint hemorrhage, with partial fusion in the submembrane along the left main bronchus, and spreading to the opening of the left upper lobe (before treatment); B, bronchoscopic image showing no hemorrhage (6 weeks after the treatment).

3. Discussion

The wide range of clinical manifestations of PTU-induced vasculitis, including mild forms with rash and/or arthralgia or severe forms with pulmonary or renal involvement, can be life-threatening if these conditions remain unrecognized and untreated. In some cases, PTU-induced AAV can be almost entirely limited to the skin (3) or to the lung (11). The most common pulmonary manifestation is alveolar hemorrhage, but nonspecific interstitial pneumonia, acute respiratory distress syndrome, vasculitic upper airways, pulmonary infiltrates, and hilar adenopathy are also seen (8, 12). Because of its variable clinical presentation and rarity, arriving at the diagnosis may be challenging, and delayed diagnosis is not uncommon without suspicion (11). PTU is responsible for the majority of cases and p-ANCA immunofluorescent staining shows a predominant ANCA pattern (4).

Although ANCA has been proposed to play a role, the etiology of PTU-induced vasculitis remains unclear. Most patients with positive p-ANCA have anti-MPO antibodies at the same time (13). It has been hypothesized that PTU can react with MPO to form reactive intermediaries that promote autoimmune inflammation and vascular damage (14). The coexistence of MPO-ANCA with antilactoferrin and/or antielastase antibodies is characteristic of vasculitis associated with PTU or hydralazine exposure (15). In our case, we also found the coexistence of MPO-ANCA and PR3-ANCA, although the latter was weakly positive.

The pathogenesis of PTU-induced vasculitis is not well elucidated. Human thyroid peroxidase (TPO) and MPO are members of the same gene family that have similar nucleotide and amino acid sequences (16). It is believed that patients with thyroid diseases and positive TPO antibodies can develop cross-reactivity to MPO. Others suggest that neutrophils, perhaps those activated by a viral infection, can release MPO from their granules, which converts PTU to cytotoxic byproducts (17). Another theory suggests that PTU is converted to PTU sulfonate via MPO, which can be immunogenic to T cells and then in turn activate the B cells to induce vascular injury (18). Alternatively, PTU could bind to MPO to change the heme structure of the enzyme (19), which can then act as a hapten and allow the initiation of autoantibody formation.

DAH in primary and secondary vasculitis can occur when capillaritis develops. The clinical symptoms of DAH (dyspnea and cough) are often not specific, and although characteristic, hemoptysis is not always present. Symptoms may develop acutely or insidiously over a few days. Whether acute or chronic, anemia is a common feature in DAH. Reduced HGB or hematocrit levels over a few days without definite bleeding are major arguments for DAH, especially when associated with increasing pulmonary alveolar opacities. The diagnosis of DAH should be considered if a patient develops progressive dyspnea with alveolar opacity on chest imaging that cannot otherwise be explained (20). During bronchoscopy, blood is frequently found to be originating diffusely from the distal airways without any localized cause. Bright red fluid on bronchoalveolar lavage (BAL) is the best diagnostic evidence of DAH. Whatever the cause, the diagnosis of DAH mainly relies on BAL findings. However, intact erythrocytes in alveolar macrophages can be seen as evidence of recent alveolar hemorrhage, whereas occult and chronic alveolar hemorrhages result from increased alveolar macrophage hemosiderin content. Microbiological investigations of BAL fluid should be systematic, because DAH may accompany lung damage of infectious origin. Lung biopsy is not routinely recommended; however, ANCA searches are mandatory (20). Once DAH is diagnosed and infectious and hemodynamic causes have been excluded, AAV should be considered. Drug-induced DAH, especially by antithyroid drugs such as PTU, can be accompanied by ANCA (20).

Our patient reported here had hemoptysis and anemia associated with increasing pulmonary alveolar opacities on a CT scan and ineffective treatment with antibiotics, which led us to suspect alveolar hemorrhage. Bronchoscopy was performed at once, and diffuse segmental hemorrhage was noted. Bronchial lavage fluid revealed 98% macrophages with iron staining positive for siderophages and negative culture findings. After treatment, the bronchoscopy examination findings were normal.

The features of DAH are not specific on chest radiograph and high-resolution CT (21, 22), but can include alveolar opacities ranging from ground glass to intense consolidation on air bronchography. The opacities are bilateral, patchy, or diffuse with predominance in the perihilar areas and in the middle and lower zones of the lungs. The evolution of opacity is often very quick, with increased density in uncontrolled DAH, and rapid clearing (within 48 hours) and no sequelae when DAH regresses. The first chest CT scan taken in our patient showed diffuse alveolar infiltrates, which was diagnosed as pneumonia, but the antibiotic treatment was ineffective. However, the alveolar infiltrates disappeared rapidly as soon as the steroids were added within 1 month.

Treatment depends on the severity of the illness. Of top priority is discontinuing the PTU immediately after the diagnosis of PTU-induced AAV (8, 23, 24). Treatment with corticosteroids, immunosuppressive drugs (e.g., cyclophosphamide and azathioprine), or plasmapheresis should be reserved for patients with active and vital organ involvement such as pulmonary or renal vasculitis for improving organ function and preventing progression to severe and irreversible disease (23, 25).

In our patient, the diagnosis of ANCA-positive vasculitis associated with the PTU therapy was strongly suspected and was supported by the ANCA titers, CT and bronchoscopy findings, and clinical resolution after stopping PTU and starting corticosteroids. To our knowledge, there are no previous reports of bronchoscopy comparison before

and after treatment in the setting of PTU-induced AAV. In this case, the association between thyroid disease and ANCA-positive vasculitis probably reflects the patient's predisposition to autoimmune disease. In retrospect, arthralgia occurred in the fourth year of PTU treatment and our patient began to obtain NSAID treatment without ANCA detection. If this side effect of PTU was suspected at that time, the severe complications and need for aggressive treatment could have been avoided.

Overall, the prognosis is better in patients with PTU-induced AAV than in those without antithyroid treatment or idiopathic ANCA-associated vasculitis if detected early (24). In ANCA-positive patients treated with PTU but without overt vasculitis, discontinuation of medication usually leads to decreased ANCA titers without the need for immunosuppressive therapy. Although symptoms usually resolve when the drug is stopped or spontaneous remission occurs (26), some patients require high doses of steroids, immunosuppressant drugs, or plasmapheresis (27, 28). Fatal diseases from this condition are rare.

Physicians should maintain a high index of suspicion when patients taking PTU develop signs of vasculitis since the early diagnosis of AAV, and prompt cessation of PTU therapy may limit the associated morbidity and mortality. When patients develop progressive dyspnea with alveolar opacity on chest imaging that could not be explained otherwise, "alveolar hemorrhage" should be an important differential diagnosis. Early diagnosis of AAV and prompt discontinuation of PTU are essential for improving patient outcomes.

PTU-induced diffuse alveolar hemorrhage associated with ANCA without any other autoimmune diseases as seen in the present case is extremely rare. Early diagnosis and prompt, correct treatment is challenging for clinicians. Here we emphasize that patients treated with PTU should be closely observed and monitored for their thyroid state and the development of ANCA and systemic disease consistent with vasculitis, which should be considered in the differential diagnosis of such cases.

Footnotes

Authors' Contribution: Ning Li designed the study; Shihai Sun and Xiaosheng Li performed the study; Weina Guo and Zhongliang Guo performed the bronchoscopy; Lei Zhang and Jie Han analyzed the data; Bo Chen and Xiaoqing Yang wrote the paper. All authors read and approved the final manuscript.

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