Propylthiouracil-induced Bronchiolitis Obliterans Organizing Pneumonia

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Abstract

Propylthiouracil (PTU) is commonly used to treat hyperthyroidism. However, it is also associated with a number of adverse events. In particular, pulmonary complications, although rare, can be serious. Therefore, early detection is paramount. We herein describe a first case of PTU-induced bronchiolitis obliterans organizing pneumonia (BOOP) pathologically confirmed on a surgical lung biopsy. The present case shows that early detection coupled with the immediate withdrawal of PTU can lead to a successful resolution of symptoms and radiographic abnormalities without the need for corticosteroids. Although rare, PTU-induced BOOP should be considered in the differential diagnosis of pulmonary opacity in patients receiving PTU therapy.

Key words: propylthiouracil, interstitial pneumonia, bronchiolitis obliterans organizing pneumonia

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Introduction

Propylthiouracil (PTU) is commonly used to manage hyperthyroidism. However, it is associated with a number of adverse events, including pulmonary complications, which, although rare, can be serious (1).

Five cases of PTU-related interstitial pneumonia have been reported to date (2-5), one of which suggested a possible bronchiolitis obliterans organizing pneumonia (BOOP)-like pattern on a transbronchial lung biopsy (5). We herein describe the first known case of PTU-induced BOOP that was pathologically confirmed on a surgical lung biopsy.

Case Report

In June 2012, a 62-year-old woman presented with a 2-month history of a dry cough. She also complained of dyspnea on exertion occurring during the two weeks prior to the assessment. She did not report sputum, fever or other flu-like illnesses. She had never smoked and had no specific occupational history. Eight months before presentation, she was diagnosed with Graves' disease and had been treated

with PTU (200 mg/day) since that time. She did not have any other medical conditions and was not taking any other medications. Chest auscultation revealed inspiratory crackles in both lung bases.

A chest radiograph showed bilateral areas of patchy alveolar opacity, primarily in the lower lobes of the lungs (Fig. 1A). High-resolution CT revealed multiple areas of subpleural and peribronchial patchy consolidation with ground-glass opacity (Fig. 1B, C). All pulmonary function tests were normal. Laboratory tests showed a white blood cell count of 4,700/mm³ (eosinophils, 7%), a hemoglobin concentration of 13.3 g/dL, a platelet count of 293,000/mm³, an erythrocyte sedimentation rate of 37 mm/h and a C-reactive protein level of 0.2 mg/dL. The oxygen saturation on room air was 95%. The patient's serum chemistry was unremarkable, with no detectable antinuclear antibodies, rheumatoid factor or antinuclear cytoplasmic autoantibodies (ANCA). Serologic tests for atypical organisms and human immunodeficiency virus were negative. Thyroid function tests showed a free thyroxine level of 0.98 ng/dL and a thyroid-stimulating hormone level of 4.0 μ IU/mL, which were within the normal ranges.

The bronchoalveolar lavage (BAL) fluid contained 3.2×

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Figure 1. Initial chest radiographic and high-resolution computed tomography (HRCT) findings. (A) A chest radiograph showed bilateral areas of patchy opacity, primarily in the lower lung fields. (B and C) HRCT of the chest demonstrated patchy airspace consolidation, areas of ground-glass attenuation and a few focal nodular areas of consolidation.

Figure 2. The pathologic findings of the surgical lung specimens. The microscopic findings of the specimen obtained from the posterior-basal segment of the left lower lobe showed variable dense fibroblastic plugs filling the airspaces (A, Hematoxylin and Eosin staining $\times 40$; B, Trichrome stain $\times 100$).

10^5 cells/mm³, comprising 36% lymphocytes, 24% eosinophils, 2% neutrophils and 38% alveolar macrophages. The BAL fluid was negative for a polymerase chain reaction (PCR) test for *Pneumocystis jirovecii* and a multiplex PCR test (Seeplex[®] RV12 ACE detection, Seegene, Seoul, Korea) for respiratory viruses, including influenza, parainfluenza, respiratory syncytial virus, adenovirus and herpes simplex virus. A cytopathologic examination for viruses and cultures for other pathogens also yielded negative results. A transbronchial lung biopsy was attempted after the BAL procedure; however, no lung specimens were obtained due to the patient's poor tolerance. Thoracoscopic wedge resection of the left lower lobe posterior-basal segment was performed to obtain an accurate pathologic diagnosis. The lung specimen showed proliferation of scattered loose fibromyxoid tissue within the terminal bronchioles, alveolar ducts and alveoli (Fig. 2A, B) with infiltration of scanty eosinophils into the airspace and interstitium. Silver-staining for *Pneumocystis jirovecii* and a molecular pathologic PCR test for adenovirus, herpes simplex virus and cytomegalovirus in the lung tissue provided negative results.

A possible diagnosis of PTU-induced BOOP was consid-

ered based on the lung histology, the absence of other likely causes and the fact that the disease developed after PTU treatment. The PTU was withdrawn immediately. The patient was not given corticosteroids because she complained only of a dry cough and mild dyspnea. Her respiratory symptoms began to resolve one month after the PTU was discontinued. In addition, chest X-rays showed an improved picture (Fig. 3A), and CT performed six months later demonstrated the nearly complete resolution of symptoms (Fig. 3B, C). She remained in a euthyroid state without receiving any other treatment.

Discussion

It is difficult to make a definitive diagnosis of drug-induced interstitial pneumonia because the clinical, radiological and histological findings are often nonspecific. The relationship between medications and the development of related lung damage is difficult to determine, particularly in patients taking multiple medicines. Fortunately, the current patient was taking only PTU. The development of BOOP in the current patient can be attributed to PTU because: 1) the chest X-ray was completely normal only one month before she started taking PTU; 2) a comprehensive medical examination excluded other causes, including subclinical connective tissue disease or infection; and 3) the pulmonary lesions almost completely resolved following the cessation of PTU.

Drugs reactions are a known cause of BOOP, and several medications have been implicated (6). The possibility of BOOP associated with PTU has been previously suggested once (5). However, that case had some limitations: the diagnosis of BOOP was based on a transbronchial lung biopsy and the patient had been taking amiodarone, which can cause adverse pulmonary effects, including BOOP (6, 7). In contrast, the diagnosis of PTU-induced BOOP in the present case was confirmed both pathologically and clinically. The present case has a similarity with a recently reported case of PTU-induced cellular nonspecific interstitial pneumonia (NSIP) in terms of physical and radiological findings (4). However, interstitial fibrosis, which was diffusely present in

Figure 3. Follow-up chest radiograph and high-resolution computed tomography (HRCT) findings obtained six months after discontinuing propylthiouracil. (A) A chest radiograph showed the resolution of the pulmonary infiltration. (B and C) HRCT demonstrated an improvement in the previous areas of consolidation and ground-glass attenuation. Linear opacity (arrow) is present at the site of a previous thoracoscopic lung biopsy.

the NSIP case, was not observed in our case on the surgical lung biopsy.

Of the five previously reported cases of interstitial pneumonia, four were treated with PTU after the patient developed an allergic reaction to methimazole (2, 3, 5). Therefore, the development of interstitial pneumonia was thought to be related to an antecedent allergic reaction to methimazole in a patient taking PTU. However, both our case and a previously reported case of NSIP (4) appear to refute this, as the patients had no prior history of methimazole treatment. A relationship between PTU and autoimmunity, including the development of ANCA, has been suggested to explain the mechanism of PTU-related interstitial pneumonia (3). However, the present patient and two previous patients (4, 5) were all negative for autoantibodies, including ANCA. Therefore, the mechanisms underlying the development of PTU-associated interstitial pneumonia remain unclear. However, it is notable that all reported cases of PTU-induced interstitial pneumonia, including the present case, occurred in patients who were more than 50 years old, as noted by Diazzi et al. (5).

Meanwhile, the different types of lung toxicity associated with PTU are similar to the various pulmonary manifestations associated with amiodarone treatment, suggesting that genetic susceptibility may play a role in determining the type of lung injury: direct injury caused by toxicity or indirect injury caused by an immune reaction (8).

The management of drug-induced BOOP depends on its severity (7). BOOP can be reversed by withdrawing the drug suspected to have caused the condition and/or by administering treatment with corticosteroids (6). The present case shows that early detection coupled with the withdrawal of

the offending drug can lead to the resolution of symptoms and radiographic abnormalities without the need for corticosteroids. On the other hand, failure to recognize the condition at the early stages may result in significant morbidity and sequelae.

In conclusion, we herein presented a case of PTU-induced BOOP in a patient with Graves' disease. Although rare, PTU-induced BOOP should be considered in the differential diagnosis of pulmonary opacity in patients receiving PTU therapy.

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

References

1. The Drug-Induced Respiratory Disease Website. www.pneumotox.com
2. Miyazono K, Okazaki T, Uchida S, et al. Propylthiouracil-induced diffuse interstitial pneumonitis. *Arch Intern Med* **144**: 1764-1765, 1984.
3. Ohwada R, Kato K, Ohmori K, et al. A man with interstitial pneumonia due to propylthiouracil. *Intern Med* **42**: 1026-1030, 2003.
4. Lee JY, Chung JH, Lee YJ, et al. Propylthiouracil-induced nonspecific interstitial pneumonia. *Chest* **139**: 687-690, 2011.
5. Diazzi C, Brigante G, Rossi G, Rochira V. Propylthiouracil-induced interstitial pneumonia in a Caucasian woman with amiodarone-induced thyrotoxicosis. *Thyroid* **22**: 325-329, 2012.
6. Epler GR. Drug-induced bronchiolitis obliterans organizing pneumonia. *Clin Chest Med* **25**: 89-94, 2004.
7. Schwaiblmair M, Behr W, Haeckel T, Märkl B, Foerg W, Berghaus T. Drug induced interstitial lung disease. *Open Respir Med J* **6**: 63-74, 2012.
8. Martin WJ 2nd, Rosenow EC 3rd. Amiodarone pulmonary toxicity. Recognition and pathogenesis (Part 2). *Chest* **93**: 1242-1248, 1988.