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Propylthiouracil-Associated Antineutrophil Cytoplasmic Antibodies Resulted Microscopic Polyangiitis and Pulmonary-Renal Syndrome ： A Case Report and Literature Review

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Abstract

Propylthiouracil (PTU) is a thionamide used for hyperthyroidism. Numbers of PTU induced adverse reactions such as leukopenia, rash, fever, arthritis, vasculitis, and lupus-like syndrome are reported. In addition, antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis during PTU therapy was reported. Pulmonary-renal syndrome is one infrequent but life-threatening presentation of PTU-associated ANCA-positive vasculitis. We report a 45-year-old woman with pulmonary-renal syndrome presented as hemoptysis, normocytic anemia, and microscopic hematuria during the treatment of Graves' disease with PTU. Her serum perinuclear-ANCA was positive and dysmorphic red blood cells were found in urinalysis. After discontinuing PTU and starting immunosuppressive agent treatment, the fever, hematuria, and pulmonary hemorrhage subsided but the p-ANCA was still present several months later. ANCA-associated pulmonary-renal syndrome may be a complication of PTU therapy. The proportion of ANCA-positive case increases with the prolongation of PTU therapy. In contrast, there are rare reports of ANCA-associated vasculitis in the other thionamide i.e. carbimazole and methimazole. Therefore, carbimazole or methimazole may be the drug of choice when long-term treatment for hyperthyroidism is required. (J Intern Med Taiwan 2005; 16: 230-235)

Key Words ：Propylthiouracil, Antineutrophil cytoplasmic antibody, Microscopic polyangiitis, Pulmonary-renal syndrome

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Introduction

Propylthiouracil (PTU), a thionamide used for hyperthyroidism, can cause a number of adverse reactions including leukopenia, rash, fever, arthritis, vasculitis, and lupus-like syndrome. Recently, small vessel vasculitis has been reported as a complication of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis during PTU therapy. Pulmonary capillaritis with diffuse alveolar hemorrhage and crescentic glomerulonephritis are two infrequent but life-threatening manifestations reported in recent ten years [1,2]. We present one case developing diffuse alveolar hemorrhage and microscopic hematuria when treating Graves' disease with PTU. Pulmonary-renal syndrome resulted by ANCA-positive microscopic polyangiitis which was associated with PTU therapy was diagnosed. We review the literature and discuss about the relationship between PTU and ANCA-associated vasculitis.

Case Report

The 45-year-old woman was a patient with Graves' disease with ophthalmopathy diagnosed in August 2000. Carbimazole was prescribed initially and stopped because of urticaria several months later. PTU, 100mg four times a day, was subscribed instead and the dose of PTU was reduced to 50 mg twice a day in June 2004. Thyroxine, 100mg per day, was used during May 2001 to Apr 2004. Besides, 9mCi I-131 was administered on Jan 2, 2004. The thyroid function test revealed thyroid stimulating hormone (TSH) <0.1 μIU/mL (normal range <6.5 μIU/mL), triiodothyronine (T3) 91.3 ng/dL (normal range 80 to 200 ng/dL), and thyroxine (T4) 5.45 ng/dL (normal range 4.5 to 12 ng/dL) in June 2004. She experienced rhinorrhea, sore throat, low grade fever, myalgia and arthralgia for one week in July 2004. High fever up to 40 ℃ and hemoptysis developed later so she visited our hospital.

Physical examination revealed pulse rate 106 /min, blood pressure 121/61 mm Hg, respiration rate 18 /min, and body temperature 37.6 ℃. The conjunctiva was not pale, and bilateral exophthalmus with lid lag was found. A grade I diffuse, elastic, and non-tender goiter was noted. On auscultation, bila-

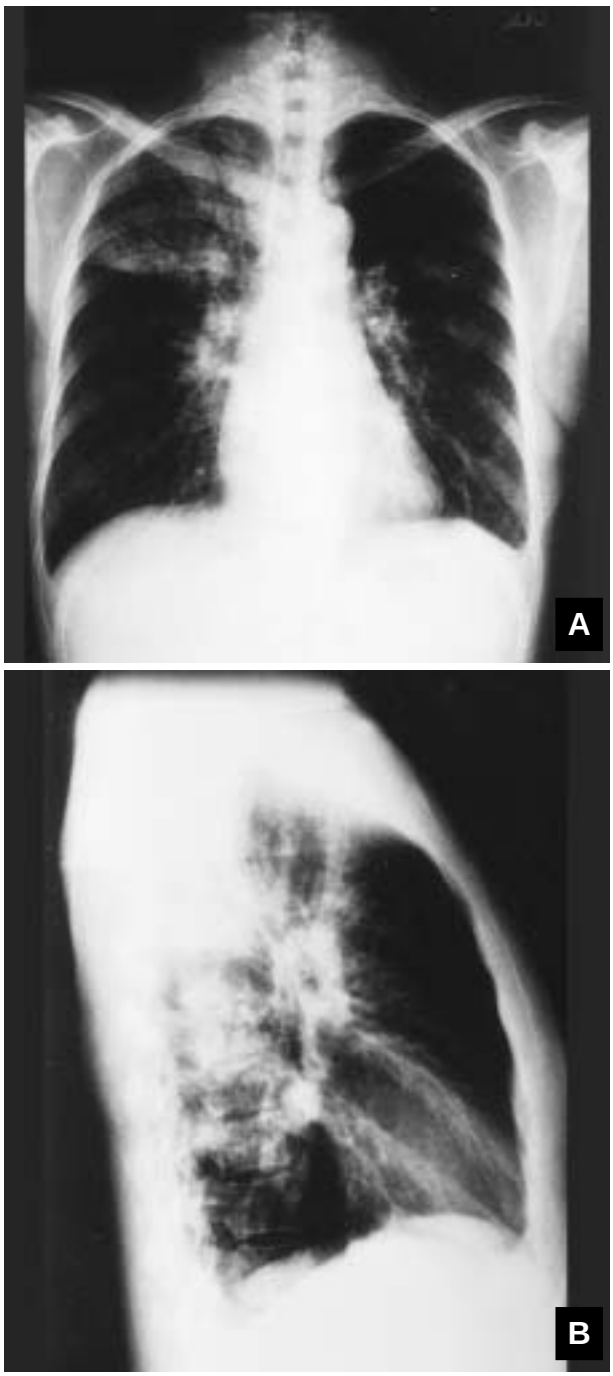

Fig.1.The chest roentgenography, PA view (A) and lateral view (B), revealed normal heart size, patchy densities at right upper and left middle lung field, linear atelectasis noted at left basal lung and blunted left C-P angle.

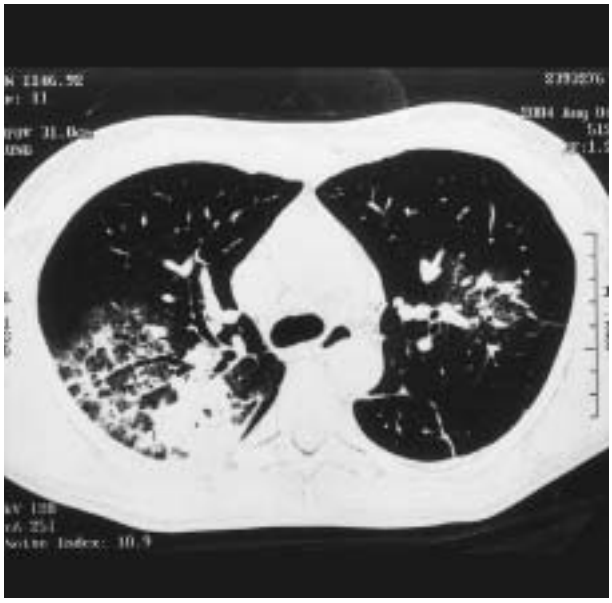

Fig.2. The chest high resolution computerized tomography revealed 1. a large segmental consolidation with air bronchogram at posterior aspect of RUL; 2. there are scattered ground glass opacities at left upper lobe and bil. fibrotic bands.

teral fine crackles were heard. There was no knocking pain over bilateral costovertebral angles. Hemogram showed hemoglobin 8.8 g/dL (normal range 13.3 ± 2 in adult female), mean cell volume of erythrocyte 86.2 fL(normal range 89 ± 10 fL), leukocyte count 3.67 K/μL (normal range 7.5 ± 3.5 K/μL) with normal differential count, and platelet count 134 K/μL(normal range 220 ± 100 K/μL). Biochemistry included blood urea nitrogen 9.7 mg/dL, creatinine 0.6 mg/dL (normal range 0.6 to 1.3 mg/dL), and C-reactive protein 8.00 mg/dL. Prothrombin time was 12.7 seconds, PT INR was 1.1, and partial thromboplastin time was 47.4 seconds compared with PTT cont. was 35.8 seconds. Urinalysis revealed no proteinuria, no pyuria and red blood cell 40-50/HPF. Free T4 was 0.55 ng/dL(normal range 0.6 to 1.75 ng/dL) and hsTSH was 1.32 μIU/mL (normal range 0.1 to 4.5). Chest roentgenography (Figure 1) revealed segmental patchy haziness over the right upper and left middle lung fields. Chest computed tomography (Figure 2) revealed repeated inflammatory change with fibrotic scar and newly developed consolidation over the right upper lung and bilateral pulmonary patchy lesion, favored pulmonary hemorrhage.

Because of pneumonia and pulmonary tuberculosis could not be excluded, empirical antibiotics with ampicillin/sulbactam, azithromycin was instituted. Her fever subsided after administration of antibiotics but the hemoptysis persisted. Sputum bacterial culture yielded Hemophilus parainfluenzae sensitive to ampicillin/sulbactam. Urinary Legionella antigen and serum Mycoplasma pneumoniae IgM antibody were both negative. Sputum acid-fast stain and tuberculosis polymerase chain reaction were also negative. Therefore, pulmonary hemorrhage other than infection was highly suggested by the finding of chest computerized tomography scan and microbiology results. Besides, microscopic hematuria with dysmorphic red blood cells disclosed glomerulopathy. Pulmonary-renal syndrome was considered. Further studies revealed noramal range C_3 (115 mg/dL), C_4 (19.3 mg/dL), negative ANA & anti-DNA, equivocal finding of antiphospholipid antibody (6.87 IU/mL), and positive p-ANCA (>10 U/mL) but negative c-ANCA (< 7 U/mL).

The clinical manifestation of pulmonary symptoms, glomerulopathy-related microscopic hematuria and the presence of p-ANCA lead to the diagnosis of ANCA-related microscopic polyangiitis. Based on the drug history, PTU is considered the trigger factor for the production of p-ANCA in our patient as previously reported.

PTU was discontinued after admission, and immuno-modifying drug including glucocorticoid, cyclophosphamide, and hydroxychloroquine were instituted. Her symptoms subsided after the treatment. After discharge, another course of methylprednisolone and cyclophosphamide pulse therapy was continued. Her condition was stable under the treatment with hydroxychloroquine ad low dose aspirin.

Discussion

In our patient, PTU was used with high dose (400 mg per day) for 3.5years due to refractory hyperthy-

roidism. She developed alveolar hemorrhage and microscopic hematuria associated with p-ANCA during PTU therapy. After withdrawal of PTU and administration of immunosuppressive therapy, all symptoms resolved, and the followed clinical course was satisfactory.

The type of ANCA in almost all PTU-associated vasculitis was p-ANCA. P-ANCA-associated microscopic polyangiitis characterized by pauci-immune necrotizing small vessel vasculitis without evidence of necrotizing granulomatous inflammation was found in our case. The prevalence of microscopic polyangiitis is around 2.4 (0.9 to 5.3) per million and the average age at onset is 53 year. Microscopic polyangiitis has renal involvement in 90% of cases accompanied by a variety of other organ involvement and is the most common cause of the pulmonary-renal syndrome[3].

ANCA, in fact, can be identified by indirect immunofluorescence and ELISA techniques. Two classical patterns have been described by indirect immunofluorescence. One pattern is cytoplasmic fluorescence pattern (c-ANCA) and the other is perinuclear pattern (p-ANCA), just positive in our case. By ELISA method, c-ANCA usually reacts with proteinase 3, whereas p-ANCA reacts not only with myeloperoxidase but also with bacterial / permeability increasing protein, cathepsin, and other myeloid protein that are found within azurophilic or primary granules of polymophonuclear leukocytes. Most laboratories usually test for proteinase 3, and myeloperoxidase because they have been related to vasculitis. This explains why some patients are ANCA positive by indirect immunofluorescence but negative by ELISA.

The etiology of ANCA-positive vasculitis is unknown, but it has been suggested that PTU may be one etiologic factor[4]. Dolman et al first reported detection of ANCA from six female patients who developed evidence of vasculitis during PTU treatment of hyperthyroidism[5]. Harper et al also reported a patient treated with PTU who developed an ANCA-positive vasculitis with glomerulonephritis and pulmonary hemorrhage[2]. In addition, Harper et al reviewed 13 cases of ANCA-associated pauci-immune glomerulonephritis associated with PTU, of which two were in children[2]. From the analysis, a female predominance (69%) and a large age variation (11to 82 years) were noted. The duration of PTU use in these reports ranged from one week to 84 months. Only two patients had deterioration of renal function. Both patients were treated with prednisolone and discontinuation of PTU. But cyclophospamide was only applied in one of them.

Among the reported cases and previous studies in the literature, nearly 80% of p-ANCA positivity occur in female patients, partly because female are predominant in patients with hyperthyroidism, who need PTU therapy. Age of ANCA-positive patient distributes from children to elders but age 30 to 60 years seems predominant. Clinical manifestations could be presented all over the body due to vasculitis, include alveolar hemorrhage, renal insults such as microscopic hematuria or proteinuria, serositis, cutaneous lesions, arthralgia and fever. The kind of vasculitis is concluded by serological ANCA tests and is definitely diagnosed by pathology. In addition to PTU discontinuation, immunosuppressive drug including corticosteroid and cyclophosphamide are the mainstay of treatment currently.

In contrast, there are only seldom reports about ANCA-associated vasculitis triggered by other kinds of thionamide i.e. carbimazole and methimazole [6-8]. Sera et al analyzed 119 serum samples from 117 Japanese patients with Graves′ disease treated with either PTU(n=56) or methimazole (n=21), as well as untreated patients (n=42)[9]. Myeloperoxidase ANCA (MPO-ANCA) was negative in all patients treated with methimazole and untreated patients. However, MPO-ANCA was detected in 37.5 % of patients treated with PTU. The proportion of patients positive for MPO-ANCA increased with the prolongation of PTU therapy but did not correlate with age,

gender and positive anti-thyroperoxidase antibody. Besides, radioactive iodine used in our patient was not correlated with ANCA-autoimmunity and vasculitis in review literature.

In recent one large cross-sectional study, Harper et al also found that the patients with Graves' disease treated with PTU were more likely to be ANCA-positive compared with those treated with carbimazole and normal controls (PTU 33.3%, carbimazole 15.9%, and controls 4.6%)[10]. The above two studies supported that the development of ANCA was associated with PTU usage to a greater extent than carbimazole or methimazole usage.

In addition to the Western and Japanese data, Huang et al set a retrospective study in Taiwanese, and found that 31.9% of patients with Graves' disease treated with PTU were seropositive for p-ANCA, while 23.4% were seropositive for MPO-ANCA[11]. In contrast, only 7.1% of age-matched patients treated with methimazole were positive for p-ANCA, and 2.4% were positive for MPO-ANCA. The average duration of PTU treatment in p-ANCA-positive patients ranged from 4.0 ± 3.6 years to 7.9 ± 10.2 years in the English literature. The Taiwanese data showed a slightly shorter duration of PTU treatment (32.9 ± 16.3 months). Compared with p-ANCA-negative patients (19.6 ± 12.1 months), the increase of positive proportion was associated with the prolongation of PTU therapy.

The pathophysiology of PTU-induced ANCA autoimmunity is still unclear. PTU may act as a hapten-binding factor altering MPO configuration and thereby promote the development of autoantibodies in susceptible individuals[12]. PTU has been shown to accumulate in neutrophils and is oxidized by MPO and hydrogen peroxide to the reactive intermediate propyluracil 2-sulphonate, which is binding to self-peptides induces T cell sensitization[13]. These metabolites also have cytotoxic activity, leading to cell death and abnormal degradation of self-material, as well as production of autoantibodies[14,15]. Alternatively, PTU may bind to MPO, changing the heme structure of the enzyme, which may then act as an antigen[15]. There is no report of carbimazole accumulating in neutrophils or acting as a hapten.

In conclusion, ANCA-related pulmonary-renal syndrome may be a newly described complication of PTU therapy. The reviewed literature disclosed p-ANCA was positive in almost all PTU-associated vasculitis. The duration of PTU therapy is the critical factor in developing ANCA-related vasculitis but not age, gender and positive anti-thyroperoxidase antibody. Moreover, ANCA-related vasculitis are rare reported in the other thionamide i.e. carbimazole and methimazole. In concern for the association of ANCA positivity or even vasculitis with PTU, carbimazole or methimazole may be the drug of choice when long-term treatment for hyperthyroidism is required.

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Propylthiouracil 相關之抗嗜中性白血球細胞質抗體併發多發性微小血管炎及肺腎症候狀：一病例報告及文獻回顧

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摘　要

Propylthiouracil (PTU)是屬於thionamide 類治療甲狀腺功能亢進的藥物。PTU會引起許多藥物副作用，包括白血球低下、皮疹、發燒、關節炎、血管炎及類似紅斑性狼瘡症候群。另外，有使用PTU的病患發生抗嗜中性白血球細胞質抗體相關血管炎的報告。肺腎症候群是其中一個不常見但會危及生命的PTU相關抗嗜中性白血球細胞質抗體陽性的血管炎表現。本文報告一位四十五歲女性Graves′ disease患者，在接受PTU治療期間以血痰、正血球性貧血和顯微性血尿來表現的肺腎症候群。血清中的胞核旁抗嗜中性白血球細胞質抗體呈陽性，尿液也有變形紅血球的發現。在PTU停藥及免疫抑制劑的治療下，發燒、血尿和肺出血的情況都有改善，但是抗嗜中性白血球細胞質抗體仍持續陽性數個月。抗嗜中性白血球細胞質抗體相關之肺腎症候群成爲新報告的PTU併發症。回溯文獻，在使用PTU的患者，使用的期間越是延長，體內被偵測到抗嗜中性白血球細胞質抗體陽性的比率也越高。相反的，其它thionamide類的藥物，如carbimazole和methimazole，少有抗嗜中性白血球細胞質抗體相關的血管炎病例被報告。因此，在需要長期使用抗甲狀腺藥物治療甲狀腺亢進時，可以優先考慮carbimazole或methimazole。