

Single Case

Propylthiouracil-Induced Antineutrophil Cytoplasmic Antibodies-Associated Vasculitis with Renal and Lung Involvement

Albert Hing Wong^a Wei-Kei Wong^a Lai-Meng Looi^b
Jeyakantha Ratnasingam^c Soo-Kun Lim^a

^aRenal Division, Department of Medicine, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia; ^bDepartment of Pathology, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia; ^cEndocrinology Division, Department of Medicine, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia

Keywords

Antineutrophil cytoplasmic antibodies · Drug-induced antineutrophil cytoplasmic antibodies vasculitis · Propylthiouracil · Graves' disease · Vasculitis

Abstract

Propylthiouracil (PTU)-induced antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAV) is a rare and heterogeneous disease. Moreover, optimal treatment is still lacking. We described the case of a 44-year-old lady with underlying Graves' disease who had cough, blood-streaked sputum, and impaired renal function. A strongly positive anti-myeloperoxidase antibody (>200 U/mL) along with pauci-immune glomerulonephritis and pulmonary hemorrhage resulted in the diagnosis of PTU-induced AAV, given that the patient had been on PTU for 3 years. PTU withdrawal, therapeutic plasma exchanges, and oral cyclophosphamide provided favorable clinical and biochemical outcomes. She remained well on azathioprine 50 mg daily as maintenance therapy and clinically euthyroid with carbimazole 2.5 mg daily. The effective treatment for drug-induced ANCA vasculitis remains controversial, but rapid withdrawal of the offending medication should be the mainstay of treatment. In severe drug-induced ANCA vasculitis with pulmonary hemorrhage and/or life-threatening organ involvement such as kidney failure requiring dialysis, therapeutic plasma exchange with immunosuppressants is often required. In this case, we have shown that patient achieved remission after therapeutic plasma exchange with cyclophosphamide in the acute stage of treatment and remained symptom-free with azathioprine in the maintenance phase of treatment for 24 months.

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Correspondence to:
Soo-Kun Lim, limsk@ummc.edu.my

Introduction

Propylthiouracil (PTU)-induced antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAV) is a rare disease. A review article by Chen et al. [1] stated that more than 100 cases of PTU-induced AAV have been reported worldwide up until 2012. PTU-induced AAV is a heterogeneous disease which ranges from mild nonspecific constitutional symptoms to severe organ impairments such as acute kidney injury, severe pulmonary hemorrhage, and even death. Although PTU-induced AAV is milder in severity and generally carries a better prognosis than primary AAV, optimal treatment for it is still lacking even though the disease was first described in 1992. Hence, this case report will be focusing on the challenges of diagnosing a case of PTU-induced AAV with renal and lung involvement as well as its treatment.

Case Report

A 44-year-old lady with underlying Graves' disease for the past 3 years presented to a private hospital with 1-week history of cough and blood-streaked sputum. She denied having fever, dyspnea, night sweats, loss of appetite, or loss of weight. There was no history of close contact to patients with pulmonary tuberculosis.

With regard to her past medical history, she was diagnosed to have Graves' disease when she presented with palpitations, tremors, and weight loss, associated with a small diffuse goiter and a positive thyroid-stimulating hormone receptor antibody. She was commenced on PTU and was not given carbimazole or radio-iodine ablative therapy in view of pregnancy intent. She was also not keen for thyroidectomy at that juncture. Over 36 months, she remained on PTU and required a PTU dose of up to 100 mg three times a day to keep her thyroid function under control.

On presentation, she was pale but vital signs were normal. Other than exophthalmos, she was clinically euthyroid. Auscultation of lungs revealed reduced breath sounds at right lower zone. There was no skin lesion, and other physical examinations were unremarkable.

Upon admission, there was impaired renal function with serum creatinine of 137 $\mu\text{mol/L}$ and urinalysis showed protein 1+ with active urine sediments. Renal ultrasound confirmed no obstructive uropathy and structural abnormality. Based on the normal kidney function 4 months before presentation with serum creatinine of 49 $\mu\text{mol/L}$, a diagnosis of acute kidney injury was made. She was also found to be anemic (hemoglobin 8.6 g/L). Besides hemoptysis, there were no other bleeding tendency and no hemolysis. High-resolution computed tomography thorax (shown in Fig. 1) showed diffuse ground glass appearance of lung fields more severe in the lung bases on the right with irregular consolidation and associated thickening of the interlobular septae. These findings were in keeping with diffuse alveolar hemorrhage with multiple focal pulmonary hemorrhage more severe in the right lung base. Other than the presence of hemosiderin laden macrophages, bronchial aspirate was negative for granuloma, malignant cells, cultures, and mycobacterium tuberculosis PCR. Connective tissue screening was negative for complements and double-stranded deoxyribonucleic acid, but anti-nuclear antibody was positive at low titer (1:80).

Renal biopsy (shown in Fig. 2) revealed focal proliferative glomerulonephritis with glomerulitis and early crescents. There were moderate focal tubular atrophy and mild focal lymphoplasmacytic infiltrates in the interstitium. No immune deposits were detected on immunofluorescence. Hence, with a strongly positive anti-myeloperoxidase (anti-MPO) antibody (>200 U/mL), a diagnosis of ANCA-AAV with pauci-immune glomerulonephritis and pulmonary hemorrhage was made. The fact that she was on PTU which was well associated

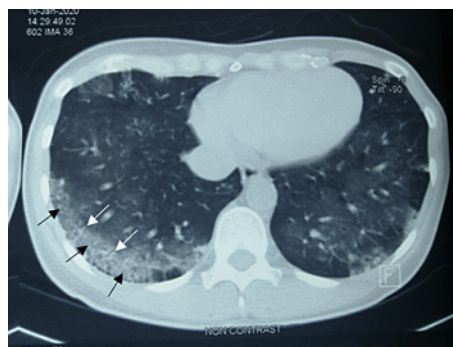


Fig. 1. HRCT of thorax findings. Diffuse ground-glass appearance of lung fields more severe in the lung bases on the right with irregular consolidation (black arrows) and associated thickening of the interlobular septae (white arrows) were observed. HRCT, high-resolution computed tomography.

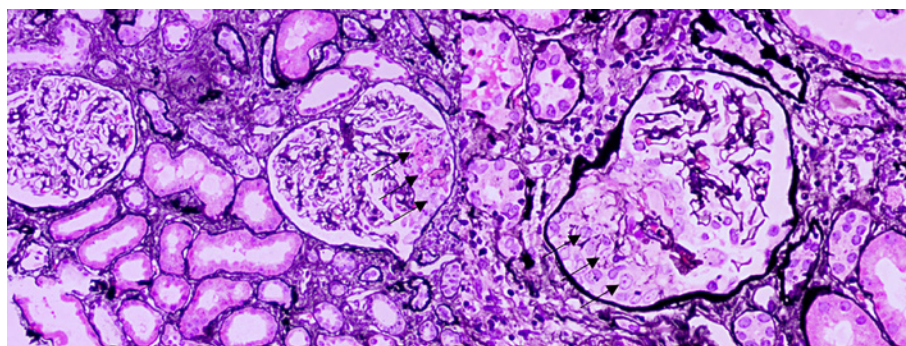


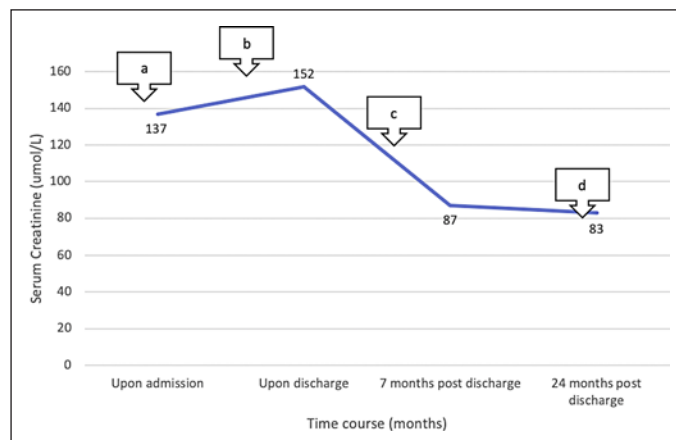
Fig. 2. Representative renal biopsy specimen findings (periodic acid silver stain, $\times 20$ magnification). Three globally sclerosed glomeruli while segmental proliferation with glomerulitis and early cellular crescents (arrow) were seen in 4 glomeruli. There were moderate focal tubular atrophy and a mild focal lymphoplasmacytic infiltrate in the interstitium. No significant vascular pathology was detected in the parenchyma. No immune deposits were detected as well.

with anti-MPO antibody, PTU-induced AAV was considered as the likely diagnosis. Thyroid-stimulating immunoglobulin, antithyroid peroxidase, and anti-thyroglobulin levels were 2.61 IU/L (<0.55), 60.4 IU/mL (0.0–35.0), and <20 IU/mL (0.0–40.0), respectively.

She was subsequently treated with pulse intravenous (IV) methylprednisolone, followed by oral prednisolone 1 mg/kg/day, and was referred to a teaching hospital for further management. In view of the rapid deterioration of kidney function (serum creatinine 140 $\mu\text{mol/L}$) and pulmonary hemorrhage, therapeutic plasma exchange (TPE) was started. She underwent 5 sessions of TPE with 1 plasma volume (1.4 L fresh frozen plasma as replacement volume over 1 h 15 min with blood flow of 100 mL/min) over 5 days. Her hemoptysis resolved after the TPE. Options for immunosuppressants were discussed, and she opted for oral cyclophosphamide over IV cyclophosphamide and rituximab. Her PTU was withheld and was switched to carbimazole at a dose of 20 mg daily which could be tapered quickly over several weeks. She was also advised against getting pregnant while she was on immunosuppression.

In the subsequent follow-ups, her proteinuria resolved within 1 month of treatment where urine protein dropped from 1+ to negative while urine protein creatinine ratio dropped from 76.1 to 46.3 mg/mmol creatinine. Urine red blood cell count took 5 months to become negative. Her serum creatinine improved over the next 7 months (137 to 87 $\mu\text{mol/L}$) (Fig. 3). She completed 3 months of oral cyclophosphamide with cumulative dose of 7.5 g and was switched to azathioprine 50 mg OD as maintenance therapy for 24 months. Anti-MPO was negative 3 months

Fig. 3. Clinical course of the present case. She was treated with pulse IV methylprednisolone, followed by oral prednisolone (**a**) before being referred to our hospital for further management. She underwent 5 sessions of TPE, and PTU was withdrawn (**b**). In the subsequent follow-ups, her serum creatinine improved over 7 months (137–87 $\mu\text{mol/L}$). She completed 3 months of oral cyclophosphamide with cumulative dose of 7.5 g (**c**) and was switched to azathioprine 50 mg OD as maintenance therapy for 24 months (**d**).



after initiation of treatment. She remained clinically euthyroid with thyroid-stimulating hormone of 1.96 mIU/L, and carbimazole was tapered down to 2.5 mg daily after 7 months.

Discussion

We reported a case of PTU-induced ANCA-AAV with kidney and lung involvement, who was successfully treated with plasma exchange and immunosuppression, in addition to withdrawal of PTU. PTU-induced AAV was strongly suspected in view of clinical presentation, presence of anti-MPO antibodies, and PTU exposure for a duration of 36 months.

PTU-induced AAV is a heterogeneous disease, and symptoms range from nonspecific constitutional symptoms such as fatigue, fever, arthralgia, and weight loss, to organ-threatening diseases including acute kidney injury, severe pulmonary hemorrhage, and death [2]. Prognosis of PTU-induced AAV has also been reported to be better as the survival rates are higher than primary AAV provided that diagnosis and withdrawal of PTU were done early [3, 4]. Even though our patient presented with pulmonary-renal syndrome with pulmonary hemorrhage, which is usually a poor prognosis indicator, she responded swiftly to few sessions of plasma exchange and immunosuppression, in addition to withdrawal of PTU. Anti-MPO turned negative after 3 months of treatment, before the cyclophosphamide was stopped. She remained euthyroid and clinically well with carbimazole even though it has been reported that carbimazole/methimazole can induce AAV but at lower rates [5, 6].

The treatment protocol for PTU-induced AAV should be individualized [7]. The most fundamental part of the treatment is to withdraw PTU immediately, and this might be all that is necessary to induce disease remission in patients who only had constitutional symptoms without organ involvement [1]. However, patients with rapidly progressive glomerulonephritis and massive pulmonary alveolar hemorrhage should receive IV pulse methylprednisolone therapy or even plasmapheresis [8, 9] which were both performed in our patient.

Randomized-controlled trials for PTU or drug-induced vasculitis are lacking, and the trials are mainly focusing on primary AAVs. The MEPEX trial showed that the 12-month risk of progression to end-stage kidney disease was reduced by 24% when plasma exchange was used compared to IV methylprednisolone in patients with newly diagnosed AAV with severe kidney failure [10]. Conversely, the PEXIVAS trial showed that plasma exchange did not reduce the incidence of death or end-stage kidney disease in patients with severe AAV with renal or lung involvement [11, 12]. Our patient received plasma exchange based on the fact that she had pulmonary hemorrhage and her hemoptysis resolved after 5 sessions of TPE.

Furthermore, pulse cyclophosphamide regimen has the same efficacy of inducing remission of AAV as daily oral regimen albeit at a reduced cumulative cyclophosphamide dose [13]. This is important as the female patients with PTU-induced AAV are usually in their reproductive age or pre-menopausal state. The RAVE and RITUXVAS trials showed that rituximab has similar efficacy when compared to cyclophosphamide for ANCA-AAV [14–16]. Other treatments that were used to induce remission in PTU-induced AAV were plasmapheresis and IV immunoglobulin [17, 18]. For maintenance therapy, Jayne et al. [19] showed that azathioprine did not increase relapse rate in AAV with threatened vital-organ function when compared to cyclophosphamide and the IMPROVE trial had shown that azathioprine is more effective than mycophenolate mofetil for remission maintenance [19, 20]. Our patient opted for oral cyclophosphamide in view of cost consideration as she has to self-finance her medical costs. She was switched to azathioprine soon after the anti-MPO antibody turned negative with relatively small cumulative cyclophosphamide dose.

The treatment of PTU-induced AAV was mainly extrapolated from the treatment of primary AAV. The optimal duration of immunosuppressive therapy for PTU-induced AAV remains unknown, but it has been suggested the duration should be shorter than that used for primary AAV, depending on the severity of organ damage [21]. While treatment of primary AAV includes induction and maintenance therapy, maintenance therapy in PTU-induced vasculitis might not be necessary as long as PTU is withdrawn [21]. In this case, the treating nephrologist has suggested and a shared decision has been made with patient to keep the azathioprine for 18–24 months before its withdrawal, in view of the clinical presentation of rapidly progressive glomerulonephritis and pulmonary hemorrhage.

Association between changes in ANCA levels and disease activity is controversial [22]. Regular follow-up of patients who are on PTU with positive ANCA without vasculitis should be done. Anti-MPO ANCA decreases with the immunosuppressants or cessation of PTU treatment [23]. Although ANCA might remain positive in some patients, it does not lead to vasculitis in a study done by Yazisiz et al. [24]. By contrast, persistent positive serum ANCA was reported by Chen et al. [25] in most of their patients at a median of 42 months. They had a risk of relapse especially if a patient had an infection and progression to ESRD even after PTU withdrawal and immunosuppressive therapy. These meant that other than titer of ANCA, affinity of ANCA is also important and high levels might be associated with PTU-induced AAV [26]. We plan to repeat the anti-MPO before stopping the maintenance therapy.

In conclusion, when a rapidly progressive glomerulonephritis case presents with ANCA positivity, drug-induced ANCA vasculitis should always be considered as part of the differential diagnosis. The effective treatment for drug-induced ANCA vasculitis remains controversial, but rapid withdrawal of the offending medication should be the mainstay of treatment. In severe drug-induced ANCA vasculitis with pulmonary hemorrhage and/or life-threatening organ involvement such as kidney failure requiring dialysis, TPE with immunosuppressants is often required. Carbimazole or definitive therapy with thyroidectomy or radio-iodine therapy will be the preferred option to PTU for treatment of hyperthyroidism in these patients. In this case, we have shown that patient achieved remission after TPE with cyclophosphamide in the acute stage of treatment and remained symptom-free with azathioprine in the maintenance phase of treatment for 24 months.

Statement of Ethics

No ethics approval was required by the University of Malaya Medical Centre Medical Research Ethics Committee. The subject had given her written informed consent for publication of the details of this medical case and accompanying images.

Conflict of Interest Statement

The authors declare that they have no conflict of interest.

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Author Contributions

Nephrologist in charge of managing the patient: Albert Hing Wong; writing – original draft and editing: Wei-Kei Wong; consulting pathologist reporting the biopsy: Lai-Meng Looi; consultant endocrinologist managing patient: Jeyakantha Ratnasingam; and supervision, review, and editing: Soo-Kun Lim. Albert Hing Wong, Wei-Kei Wong, Lai-Meng Looi, Jeyakantha Ratnasingam, and Soo-Kun Lim take responsibility that this study has been reported honestly, accurately, and transparently, and accept accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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