

Propylthiouracil induced pulmonary-renal syndrome: a case report

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ABSTRACT

Propylthiouracil (PTU) is known to induce antineutrophil cytoplasmic antibody (ANCA) seropositivity; however, small vessel vasculitis (SVV) with pulmonary and renal involvement is rare.

We present the case of an 81-year-old woman on PTU treatment due to toxic nodular goitre who developed alveolar hemorrhage and rapidly progressive glomerulonephritis.

The authors highlight the importance of early recognising drug-induced pulmonary-renal syndrome (PRS) in order to avoid unnecessary tests, a delay in the diagnosis and evolution to end-stage kidney disease or life-threatening conditions.

Keywords: Propylthiouracil; Pulmonary manifestations; Anti-neutrophil cytoplasmic antibodies; Renal involvement; Systemic vasculitis;

INTRODUCTION

Propylthiouracil (PTU) is commonly used to treat hyperthyroidism. Adverse reactions such as fever, rash, leucopenia, pneumonitis, vasculitis, and lupus-like syndrome have been largely reported^{1,2}. PTU can induce antineutrophil cytoplasmic antibody (ANCA) seropositivity (estimated from 20-64% in reported studies^{3,4}) but only few patients develop a small vessel vasculitis (SVV) associated with pulmonary-renal syndrome (PRS).

Clinical and laboratory presentation of PRS can be polymorphic, nonspecific and represents a challenge

for clinicians. Drug-induced effects should be always considered in differential etiologic diagnosis of vasculitis.

We present the case of a patient who developed alveolar haemorrhage and rapidly progressive glomerulonephritis due to PTU treatment.

CASE REPORT

An 81-year-old non-smoker woman was admitted to our hospital because of cough and haemoptysis. These symptoms had started one week before the admission and had gradually become more severe. A toxic nodular goitre had been diagnosed 10 years before and she was on PTU 200 mg daily, since then. She had previously refused radioactive iodine treatment.

No medical history of fever, constitutional symptoms, and signs of joint, ocular, skin involvement or chronic organ failure was reported.

Routine laboratory tests performed one year before the admission were normal.

On admission, blood pressure was 110/75 mmHg, heart rate 103 bpm and body temperature 36°C. Respiration rate was 20 breaths for minute and oxygen saturation was 98% in room air.

Auscultation of the lungs revealed bibasilar crackles while the remaining physical examination was unremarkable.

Laboratory tests showed normocytic normochromic anaemia haemoglobin 8.1 g/dL, reference range 11.5-15.5 g/dl, normal white blood cell and platelet counts, increased C-reactive protein 1.6 mg/dL (< 0.5 mg/dL) and erythrocyte sedimentation rate 30 mm/h (< 20 mm/h). Protein electrophoresis was unremarkable. Thyroid function, liver function and coagulation tests were normal. Viral hepatitis and HIV serology were negative as well. Renal function tests showed increased blood urea nitrogen (120 mg/dL, reference range 17-

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FIGURE 1. Chest x-ray showed bilateral heterogeneous pulmonary opacities (A) and chest CT scan revealed multifocal areas of ground-glass opacities and bibasilar honeycomb lung (B-C)

-43 mg/dL) and creatinine (2.57 mg/dL, reference range 0.51-0.95 mg/dL). Urinalysis revealed haematuria (erythrocytes 401/L, (< 22/L) and proteinuria (100 mg/dL) quantified in the urinalysis as 2,7g/day.

Chest x-ray showed bilateral heterogeneous pulmonary opacities (Figure 1. A) and chest computerized tomography (CT) scan revealed multifocal areas of ground-glass opacities and bibasilar honeycomb lung (Figure 1. B-C).

Flexible bronchoscopy (FB) revealed hyperaemic bronchial mucosa and haemosiderin-laden macrophages were isolated in bronchoalveolar lavage fluid.

Ultrasound examination of the kidneys was normal.

PRS was suspected and perinuclear ANCA (p-ANCA) with antimyeloperoxidase antibody (MPO 126.4 U/ml; < 20 U/ml) were found to be positive; cytoplasmic ANCA (c-ANCA), anti-nuclear antibody, antiglomerular basement membrane antibody and remaining immunological tests were negative.

Renal biopsy revealed SVV with fibrinoid necrosis with inflammatory mononuclear-cell infiltration, cellular crescents, rupture of Bowman's capsule, focal segmental glomerulosclerosis, cortical interstitial fibrosis and tubular atrophy (Figure 2. A-B-C-D).

PTU-induced p-ANCA-positive SVV with pulmonary and renal involvement was diagnosed.

PTU treatment was stopped; methimazole (5 mg daily), pulse methylprednisolone (500 mg daily during 3 days) followed by corticotherapy (1 mg/kg/daily) and intravenous pulses cyclophosphamide (0.5 g/m² biweekly) were started. Due to its immunomodulatory properties and in order to prevent *Pneumocystis jirovecii* infection, cotrimoxazole was started too. Symptoms, clinical and laboratory findings improved

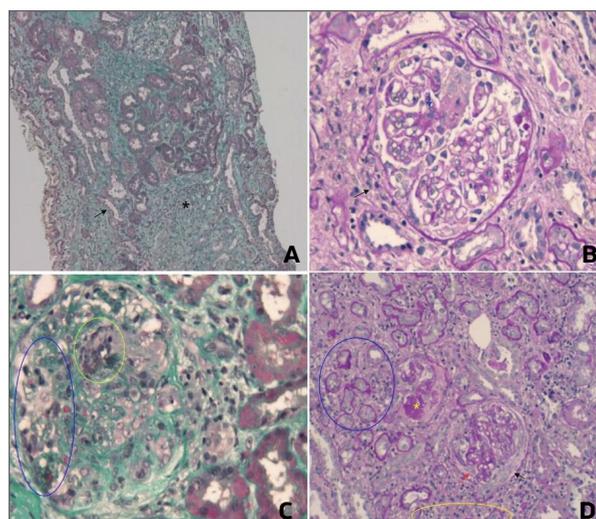


FIGURE 2. A) Masson's trichrome (MT) 100X: Interstitial fibrosis areas (black star) and tubular atrophy (black arrow). B) Periodic acid-Schiff (PAS) 400x: Glomerulus with fibrinoid necrosis (blue arrow) and cellular crescent (black arrow). C) MT 400x: glomerulus with fibrinoid necrosis (green oval) and cellular crescent (blue oval). D) PAS (200x): glomerulus with fibrin crescent formation and partial sclerosis of the new capillary (yellow star); glomerulus with fibrocellular crescent (black arrow) and Bowman's capsule rupture (red arrow); tubular atrophy and interstitial fibrosis (blue oval); mononuclear inflammatory cell infiltrate surrounding glomeruli (yellow oval)

(Hemoglobin 10.5 g/dL; Urea 89 mg/dL; Creatinine 1.6 mg/dL; 24 hour-proteinuria 0.95 g/day) within two months of PTU withdrawal. No leukopenia occurred and ANCA titre decreased (36.23 U/ml) after six months of immunosuppressive therapy induction. Azathioprine (2 mg/kg/day) was used as maintenance therapy.

DISCUSSION

PRS is most commonly due to SVVs, such as ANCA-related vasculitis (ARV), Goodpastures disease, IgA nephropathy/Henoch-Schönlein purpura and systemic lupus erythematosus and there is certainly an overlap in clinical and laboratory phenotypes among these SVVs.

ARV includes granulomatosis with polyangiitis, microscopic polyangiitis, eosinophilic granulomatosis with polyangiitis, renal-limited vasculitis and drug-induced vasculitis. ARV may present with severe organ involvement; this is why identification of potentially

reversible causes, such as drugs, is very important.

The drugs most frequently associated with ANCA seropositivity are antithyroid agents such as PTU and, less frequently, methimazole and carbimazole. It has been reported that patients receiving long-term PTU treatment may develop antibodies directed against neutrophil perinuclear antigen (Myeloperoxidase; p-ANCA), neutrophil cytoplasmic antigen (Proteinase 3; c-ANCA) or against other neutrophil antigens such as human leucocyte elastase, lactoferrin, cathepsin G, azurocidin and bactericidal/permeability-increasing protein^{3,5}.

Other drugs implicated in ANCA seropositivity are penicillamine, hydralazine, minocycline, allopurinol, procainamide, thiamazole, clozapina, phenitoin, rifampicin, cefotaxime, sulfasalazine, ciprofloxacin, isoniazid and indomethacin⁶.

PTU induced p-ANCA vasculitis was first reported in 1993⁷ and the physiopathological mechanism still remains uncertain. It seems that PTU accumulates in neutrophils, binding and potentially modifying MPO antigens, and leading to the formation of autoantibodies in susceptible patients.

ANCA titre usually decreases after PTU withdrawal but in some cases can remain elevated without evidence of SVV.

The duration of PTU-treatment prior to clinical presentation ranged from 1 week to 7 years⁸.

Drug induced ANCA-associated vasculitis can be associated with constitutional symptoms, fever, arthralgias, arthritis, cutaneous vasculitis and, less frequently, with rapidly progressive glomerulonephritis and alveolar hemorrhage.

Renal involvement is the most common manifestation⁹ and can occur with nephritis and acute failure.

Alveolar hemorrhage is a potentially life-threatening condition: our patient had haemoptysis and anemia but FB showed no active hemorrhage.

The diagnosis of PTU-induced vasculitis in our patient was made by observation of clinical findings, high index of suspicion of PRS, the presence of p-ANCA seropositivity, renal histology and clinical and laboratory improvement documented after PTU discontinuation and immunosuppressive therapy.

The optimal management of drug-associated ANCA vasculitis consists in discontinuation of the triggering agent and, in case of lung and kidney involvement, initiation of corticosteroids and cyclophosphamide. In case of advanced kidney failure, dialysis-dependency or diffuse alveolar hemorrhage, plasmapheresis can be

eventually indicated¹⁰.

Fatalities are rare¹¹ and PTU-induced ANCA SVV has a better prognosis than primary ANCA-associated SVV¹².

We report this case of PTU-induced PRS to increase physicians awareness of the potential risk for the development of drug-associated ANCA vasculitis.

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