Propylthiouracil-associated rapidly progressive crescentic glomerulonephritis with double positive anti-glomerular basement membrane and antineutrophil cytoplasmic antibody: the first case report

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Abstract We report a case of propylthiouracil (PTU)-induced double antineutrophil cytoplasmic antibody (ANCA) and anti-glomerular basement membrane antibody (anti-GBM antibody) disease causing pulmonary-renal syndrome in a 35-year-old Thai woman with 10-year history of PTU treatment for thyrotoxicosis. She developed clinical symptoms of vasculitis upon receiving long-term PTU treatment. Prednisolone treatment and the switching from PTU to methimazole resulted to short-term clinical improvement. Nevertheless following termination of steroid treatment, she developed recurrent pulmonary hemorrhage and rapidly progressive glomerulonephritis. The kidney biopsy showed crescentic glomerulonephritis with linear IgG deposit on the glomerular basement membrane although transbronchial lung biopsy showed no immune deposit along the alveolar basement membrane. Serum testing for p-ANCA was positive and western blot showed positive antibody to the alpha-3 chain of collagen type IV. Both ANCA and anti-GBM antibody may play a role in the development of end organ damage. To facilitate early and specific intervention, clinicians should be aware of the propensity of PTU to cause lupus-like syndromes with renal involvement. In patients

with PTU-induced ANCA-associated glomerulonephritis, serum anti-GBM antibody test may be useful in the early diagnosis of double positive antibodies disease and plasmapheresis should be performed without delay.

Keywords Anti-glomerular basement membrane antibody · Antineutrophil cytoplasmic antibody · Crescentic glomerulonephritis · Propylthiouracil

Introduction

Propylthiouracil (PTU)-induced autoimmune syndromes in thyrotoxicosis patients have previously been reported [1]. Some patients present with vasculitis and/or lupus-like syndrome. Perinuclear-ANCA (P-ANCA) can be found in both PTU-induced lupus and vasculitis. In severe cases, PTU-induced ANCA-associated vasculitis can present with pulmonary-renal syndrome [2–4]. It has been shown that PTU is implicated in 80–90 % cases of vasculitis induced by antithyroid drugs, while cases related to other drugs, such as methimazole [5], carbimazole [6] and benzylthiouracil [7] are less frequent. Renal involvement in 19 case series of patients from China with PTU-associated ANCA-positive vasculitis was heterogeneous, and nearly half of the patients had renal immune complex deposition [8]. We herein report the first case of antithyroid drug-associated double ANCA and anti-GBM antibody disease causing pulmonary-renal syndrome.

Case report

A 35-year-old Thai woman who had been diagnosed with Grave's disease and received PTU therapy for 10 years

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presented to a local hospital with hemoptysis, dyspnea, low grade fever and bilateral arthritis of the wrists and proximal interphalangeal joints for 2 weeks. Prior to this episode she was taking PTU 200 mg daily. The patient was clinically euthyroid and had no exophthalmos. She had a small diffuse goiter without any associated thrill or bruit. She had no skin lesions, scleritis, hearing loss, oral ulcer, abdominal pain, neurological deficit or peripheral edema.

Chest X-ray revealed diffuse alveolar infiltration (Fig. 1a) and PTU-induced pulmonary vasculitis was diagnosed (BVAS 13). Urine examination revealed RBCs of 50/HPF, WBCs of 1–2/HPF and 1+ protein which suggested glomerulonephritis. Blood tests showed a BUN of 14 mg/dl, creatinine of 0.8 mg/dl. ANCA and anti-GBM antibodies testing were not available at the time. PTU was withdrawn and prednisolone 45 mg/day (0.8 mg/kg/day) was given for 1 month. Her hemoptysis and arthritis subsided (BVAS 3). Urinary analysis showed trace proteinuria and RBCs of 10–15/HPF after steroid treatment. Due to clinical improvement and cessation of PTU, steroid therapy was stopped. Then, I^{131} and methimazole 15 mg/day was prescribed to control hyperthyroidism. Four months later, she developed recurrent hemoptysis and dyspnea on exertion. Prednisolone was administered again without improvement. Two days prior to admission she noticed less frequent urination and more amounts of blood in the sputum and, therefore, came to Ramathibodi hospital. She denied any history of skin rash, photosensitivity, hair loss, nocturia, hematuria and leg edema. Physical examination revealed BP of 170/80 mmHg, pulse 100/min, body temperature 37.0 °C, respiratory rate 32/min and arterial oxygen saturation; 91.0 % while on O_2 5 l/min via nasal cannula. She was conscious but was pale and short of

breath. There was no leg edema or jugular vein engorgement. Fine crepitations were heard in both lungs. There was no organomegaly or joint swelling. Complete blood count showed Hb of 6.8 g/dl, white blood cell of 8,880/ mm^3 with normal differential count and a platelet count of 144,000/ mm^3 . Urinalysis revealed protein 3+, WBC 3–5/HPF and RBC >100/HPF with no acanthocytes. She had a BUN of 96 mg/dl, serum creatinine of 6.5 mg/dl and CRP level of 14.1 mg/l. Thyroid function tests suggested sub-clinical hyperthyroidism. The serologic laboratory results showed negative antinuclear antibodies, hepatitis B surface antigen, hepatitis C antibody, anti-HIV and c-ANCA. However, p-ANCA antibody was positive by indirect immunofluorescence (titer >1:160) and positive anti-myeloperoxidase (MPO) antibody by enzyme-linked immunosorbent assay (ELISA) (93.2 U/ml; normal range 0–9 U/ml) were found. Serum complement 3 and 4 levels including CH_{50} were normal. Her chest X-ray (Fig. 1b) showed mild cardiomegaly and bilateral alveolar infiltration. The bronchoalveolar lavage and transbronchial biopsy revealed hemosiderin-laden macrophages without specific pathogen and immune deposition.

A clinical diagnosis of rapidly progressive glomerulonephritis (RPGN) and pulmonary hemorrhage was made (BVAS 18). The patient received methylprednisolone 1 gram intravenously for 3 days followed by oral prednisolone 1 mg/kg/day with slowly tapered to 20 mg at 3 months and monthly pulse intravenous cyclophosphamide 500 mg/ m^2 for 6 courses. Hemodialysis was started due to volume overload and uremia. Kidney biopsy revealed total number of 24 glomeruli, cellular and fibrocellular crescents in 20 glomeruli with 6 global and 2 segmental sclerotic glomeruli. Granulomatous inflammation was not found. Mild

Fig. 1 Chest X-ray. **a** Chest X-ray at first presentation shows mild cardiomegaly and diffuses alveolar infiltration. **b** Chest X-ray upon recurrence of clinical symptoms showed marked cardiomegaly and bilateral diffuse alveolar infiltration

tubular atrophy with focal lymphocytic interstitial infiltration and fibrosis were also present. The immunofluorescence study showed linear deposition of IgG along the GBM compatible with anti-GBM disease (Fig. 2). The kappa and lambda light chain immunoperoxidase stainings were negative (data not shown). Anti-GBM-induced severe crescentic glomerulonephritis was then diagnosed and confirmed by positive serum anti-GBM antibodies against alpha-3 chain of collagen type IV by western blot analysis (Fig. 3). Despite plasmapheresis of 1 plasma volume for 14 consecutive days, the patient remained on dialysis for 10 weeks after which her renal function settled with a serum creatinine of 4.9 mg/dl (eGFR of 10 ml/min/1.73 m²) (BVAS 3). She received maintenance immunosuppressive therapy with azathioprine and low dose oral prednisolone without any recurrence of clinical symptoms but eventually progressed to end stage renal disease 2 years later (BVAS 3). The MPO-ANCA titer gradually decreased to 42.2 U/ml (normal 0–9 U/ml) at 1 year and 2.4 U/ml (normal 0–9 U/ml) 2 years later.

Discussion

To our knowledge and after performing a literature review, this is the first case report of PTU-associated double positive antibodies disease. This patient had received PTU therapy for a long period of time and, therefore, had a high possibility of development of ANCA-positive vasculitis syndrome [9]. The onset of vasculitis can vary from 7 months to 6 years after long-term use of PTU. Her initial clinical manifestations of fever, polyarthritits, glomerulonephritis and pulmonary hemorrhage indicated vasculitis induced by PTU. The diagnostic criteria of PTU-induced ANCA-associated vasculitis were often defined as follows: (1) the signs and symptoms of vasculitis were temporally related to using PTU, and regressed with discontinuation; (2) serum ANCA was positive, especially in those with multi-antigenicity; and (3) medical conditions that mimicked vasculitis were excluded, especially infections and malignancies, and other definable types of vasculitis [10]. The initial clinical response to steroid alone without

Fig. 2 Kidney pathology. **a** The low magnification of the biopsy shows cellular crescents in 3 glomeruli with interstitial inflammation and tubular injury (PAS staining $\times 100$). **b** The high magnification of the glomerulus shows circumferential cellular crescent (H&E staining $\times 200$). **c** The glomerulus shows circumferential cellular crescent.

Discontinuation and fragments of the glomerular basement membrane (*arrow head*) are observed. Discontinuation/rupture of Bowman's capsule is noted (*arrow*). **d** Immunofluorescence staining shows linear deposits of immunoglobulin G (IgG)

Fig. 3 Western blot of serum against alpha 3 collagen type IV. Western blotting was performed with native type IV collagen antigens purified from bovine testis (*Bov*) and with recombinant human type IV collagen alpha-3 (*rA3*) and alpha-5 chain (*rA5*) NC1 domains [20]. Samples were run on 12.5 % 8 × 10 cm SDS-PAGE gels in non-reducing conditions and electroblotted to nitrocellulose membranes, using a wet system (Sigma), overnight at 30 mA. Negative controls obtained from pooled normal human serum (control negative serum) and putative low-titer samples were used at 1:20. The positive control serum (control positive serum) obtained from patients diagnosed with anti-glomerular basement membrane disease were used at

1:40–1:100. The positive band of 41 kDa monomer of recombinant human alpha-3 antigen was detected in positive control (control positive serum) and the patient's serum (*rA3* lane), which confirmed the presence of autoantibodies against the alpha 3 chain of collagen type IV [21]. These serums also bind alpha 3 chain of collagen type IV purified from bovine testis (*Bov* lane). They recognize the 45 and 28 kDa bands corresponding to dimers and monomers of the NC1 domain of type IV collagen purified from bovine testis seminiferous basement membrane [22, 23]. There was no band detected in the negative control incubated with the type IV collagen purified from bovine testis

plasmapheresis also suggested vasculitis rather than anti-GBM disease. PTU treatment was withdrawn and methimazole in combination with I^{131} was given. However, relapse of pulmonary hemorrhage and glomerulonephritis after steroid cessation occurred. Treatment with methimazole has also been reported to be associated with positive ANCA although the prevalence is much lower [5, 11, 12]. Given the chemical relating between PTU and methimazole, cross-reactivity between the two drugs regarding to development of ANCA-positive vasculitis has been previously reported [13].

It is also possible that the drug somehow triggers a predisposition to development of the disease. As a result, the disease process may progress even though antithyroid drugs were withdrawn. In supporting this hypothesis, the occurrence of ANCA vasculitis following cessation of the drug for long period of times has been previously described [14]. Alternately, the patient may have a primary double positive antibodies disease unrelated to PTU.

The kidney biopsy later on showed the classical pathology of anti-GBM-induced crescentic glomerulonephritis with deposition of antibodies in a linear pattern on the GBM. Autoantibodies to the NC1 domain of the alpha-3 chain of type IV collagen (the Goodpasture antigen) were also demonstrated by western blot in her serum although we did not detect any immunoglobulin deposition in the alveolar basement membrane. One possible mechanism of renal injury in this case could be due to the exposure of the GBM antigens by vasculitis which stimulated pathogenic

anti-GBM antibodies causing crescentic glomerulonephritis as suggested by Serratrice et al. [15].

Hyperthyroid patients treated with PTU should be placed under vigilant observation by monitoring their urinalysis and serum creatinine level; particularly in cases of prolonged treatment and those with systemic symptoms suggestive of vasculitis. Early withdrawal of PTU and administration of immunosuppressive agents might improve the prognosis [4]. In patients with severe side effects, it may be necessary to initiate definite treatment for hyperthyroidism such as thyroid surgery or radioactive iodine ablation because all antithyroid drugs—methimazole, carbimazole, PTU, and benzylthiouracil have been associated with ANCA-positive syndromes.

Furthermore, in patients with PTU-induced ANCA-associated glomerulonephritis, serum anti-GBM antibody testing may be useful in the early diagnosis of double positive antibody disease and plasmapheresis should be performed without delay. A kidney biopsy can be performed to establish a histopathological diagnosis when the patient's condition has stabilized, especially after improvement of pulmonary hemorrhage.

The clinical outcome of patients with double positive antibodies who present with severe renal failure is varied. Most patients receive immunosuppressive treatment and plasma exchange. Some studies reported good outcomes [16] but others found that most patients had poor outcomes [17]. A recent larger series reported poor prognosis of these patients and recovery from renal failure was rare [18, 19].

The different outcomes of treatment between the studies are not well understood. In one study by Rutgers et al., they compared histological and clinical features of patients with both ANCA and anti-GBM antibodies to those with ANCA or anti-GBM alone. Findings showed that the mean ages of double positive and MPO-ANCA patients were older than anti-GBM patients. However, double positive patients had poor renal survival similar to anti-GBM patients and worse than patients with MPO-ANCA only [19]. In our patient, whose initial presentations were presented at a younger age, the presence of double positive disease may be due to her PTU treatment.

We described the first case of pulmonary-renal syndrome as a complication of PTU-associated ANCA and anti-GBM antibodies syndrome. Early diagnosis by serological testing of these two antibodies should be performed prior to obtaining a definite pathological diagnosis with kidney biopsy. Prompt treatment with PTU cessation, immunosuppressions and plasmapheresis may help to improve the prognosis of this disease.

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Conflict of interest The authors declare that they have no competing interests.

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