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CASE REPORT

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Propylthiouracil-induced antineutrophil cytoplasmic antibody-associated crescentic glomerulonephritis in a patient with a predisposition to autoimmune abnormalities

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Abstract A 65-year-old woman with a history of primary biliary cirrhosis was diagnosed as having myeloperoxidase-antineutrophil cytoplasmic antibody (MPO-ANCA)-associated crescentic glomerulonephritis (GN) during propylthiouracil (PTU) therapy for Graves' disease. Antinuclear antibodies, as well as various thyroid-associated autoantibodies, had been detected since the diagnosis of Graves' disease was made. The patient carried human leukocyte antigens (HLAs) DR4 and DR9, the two HLA haplotypes that have been reported to be related to ANCA-associated vasculitis. Withdrawal of PTU and the administration of prednisolone resulted in a decrease in the titer of MPO-ANCA, together with an improvement in renal function. It is suggested that in addition to the PTU therapy, her genetic predisposition to autoimmunity had played a role in the production of MPO-ANCA and the development of crescentic GN.

Key words Antineutrophil cytoplasmic antibody (ANCA) · Autoimmunity · Crescentic glomerulonephritis (GN) · Primary biliary cirrhosis (PBC) · Propylthiouracil (PTU)

Introduction

Propylthiouracil (PTU) has been known to be associated with the antineutrophil cytoplasmic antibody (ANCA), which has been postulated to play a role in the pathogenesis of systemic vasculitis and crescentic glomerulonephritis (GN). Previous studies showed that positivity for ANCA, as well as the development of crescentic GN or vasculitis, occurred in a subgroup of patients treated with PTU, which indicates that etiologic and genetic factors may be involved in the PTU-induced ANCA production and the subsequent onset of the above-mentioned diseases.[1,2]

We describe the case of a 65-year-old woman who developed ANCA-associated crescentic GN during PTU therapy for Graves' disease. She had a predisposition to autoimmunity, a history of primary biliary cirrhosis (PBC), and antinuclear antibodies (ANA), and various thyroid-associated autoantibodies had been detected. In addition, she carried human leucocyte antigen (HLA) haplotypes, which have been reported to be involved in the development of ANCA-associated vasculitis.[3,4] We present the clinical course of this patient, and discuss the relationship between a predisposition to autoimmunity and the development of ANCA-associated diseases during PTU therapy.

Case report

A 65-year-old woman with Graves' disease, who had been treated with PTU (300 mg/day) and triiodothyronine (20 μg/day) for 1.5 years, was admitted to our hospital in November 1999 after a 6-month history of general malaise, a 10-kg weight loss, hematoproteinuria, and recurring fever. She had been diagnosed as having PBC based on a liver biopsy, and was positive for the antimitochondrial antibody (Ab) when she was 57 years old. Her PBC had been well controlled with ursodeoxycholic acid. In July 1998, she was diagnosed as having Graves' disease, and at the same time ANA (×640) was detected in addition to various thyroid-associated Abs, although her ANCA level was not measured. Her family history was negative for autoimmune disease. The results of a physical examination on admission were unremarkable except for a fever of 37.6°C and mild edema of the legs. There was no evidence of cutaneous vasculitis, hepatomegaly, or symptoms associated with hyperthyroidism such as thyroid swelling, exophthalamus, or tachycardia. A chest radiograph and an electrocardiogram showed no abnormalities. Laboratory tests gave the following results (values in parentheses indicate the normal range): WBC, 11 000/mm^3; RBC, 350 × 10^4/mm^3;

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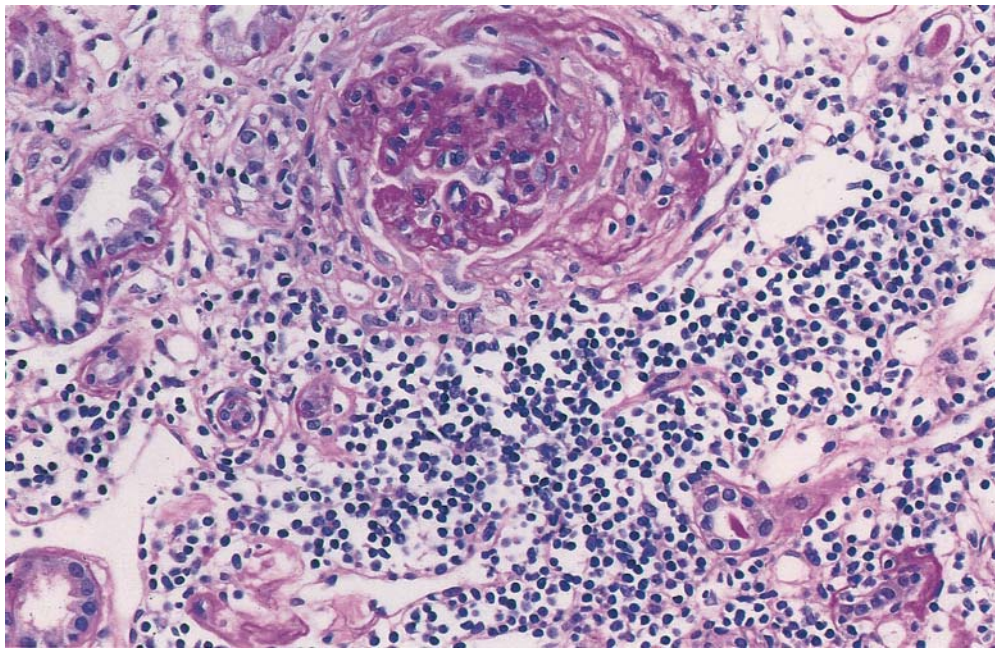

Fig. 1. Glomerulus showing fibrocellular crescents. Severe tubulointerstitial infiltration of mononuclear cells was also observed (periodic acid–Schiff stain; original magnification ×40)

Hb, 9.9 g/dl; Ht, 29.4%; platelets, $38.8 \times 10^4/mm^3$; total protein, 7.0 g/dl; albumin, 2.5 g/dl; total bilirubin, 0.5 mg/dl; creatinine, 1.0 mg/dl; serum urea nitrogen, 12.6 mg/dl; CRP, 10.4 mg/dl. The levels of serum liver transaminase and serum electrolytes were normal. The levels of serum immunoglobulins were elevated: IgG, 2823 mg/dl; IgA, 614 mg/dl; IgM, 465 mg/dl. Urinalysis showed mild proteinuria (0.63 g/day) and microscopic hematuria (RBC 20–29/HPF). Creatinine clearance was 29.4 ml/min. The titer of myeloperoxidase (MPO)-ANCA was high (312 EU/ml (<10 EU/ml)). Although the patient had no symptoms of mixed connective tissue disease, scleroderma or Sjögren's syndrome, some autoantibodies associated with these diseases were present: anti-RNP Ab, 45.0 cut-off index (COI) (<5 COI); anti-Scl-70 Ab, 6.8 COI (<5 COI); anti-SSA Ab, 14.3 COI (<7 COI). Anti-ssDNA, anti-dsDNA, anti-Sm, anti-SSB, antimitochondrial Abs, and proteinase 3 (PR3)-ANCA were absent. The levels of serum complements were normal, and circulating immune complexes and cryoglobulin were not detected. The levels of thyroid function parameters in the serum were as follows: free T4, 0.32 ng/ml (0.88–1.81 ng/ml); free T3, 4.12 ng/ml (2.2–4.1 ng/ml); thyroid-stimulating hormone (TSH), 0.13 μg/ml (1.35–3.73 μg/ml). The titers of thyroid-associated Abs in serum were as follows: antimicrosomal Ab, 1:400; antithyroglobulin Ab, 1:1600; anti-TSH receptor Ab, 28.8% (<15%); antithyroperoxidase Ab, 2.4 U/ml (<0.3 U/ml). The serological types of human leukocyte antigen (HLA) were A24/31, B39/54, Cw1/w7, DR4/9, and DQ4/9.

Malignancies and infectious diseases were ruled out based on the examination results. Since recurring fever and hematoproteinuria with high titers of MPO-ANCA were suggestive of PTU-induced ANCA-associated vasculitis or crescentic GN, the PTU therapy was discontinued, and prednisolone (60 mg/day) was started on the 23rd day after admission, when the serum creatinine level increased to 1.4 mg/dl. A renal biopsy was performed on the 29th day after admission. Light microscopy of the renal biopsy sample revealed 15 glomeruli, 5 of which were sclerosing, and 7 had fibrocellular crescents. There was severe infiltration of mononuclear cells in the interstitium (Fig. 1). Immunofluorescence microscopy showed no deposition of immunoglobulins and complements. No electron-dense deposition was found by electron microscopy. The pathological diagnosis was pauciimmune crescentic glomerulonephritis with severe tubulointerstitial nephritis. Although the patient's symptoms were suggestive of systemic vasculitis, this was not supported by renal biopsy findings.

The withdrawal of PTU and steroidal therapy resulted in a decrease in both the serum creatinine level and the titers of serum MPO-ANCA. Proteinuria and microhematuria disappeared (Fig. 2), and thyroid function was maintained within the normal range.

A second renal biopsy was performed on the 92nd day after admission, when the serum creatinine level became normal and the titer of MPO-ANCA had decreased to 59 EU/ml, which was still higher than the normal range. Light microscopy revealed 48 glomeruli, 9 of which exhibited global sclerosis. Fibrocellular and fibrous crescents were present in 9 glomeruli, and the interstitial damage was markedly improved.

Free-T3 and free-T4 levels began to increase on the 100th day after admission, and the patient was subsequently treated with thiamazole (5 mg/day). She was discharged on the 114th day after admission, when prednisolone was reduced to 20 mg/day. At that time, the titer of serum MPO-ANCA had decreased to 37 EU/ml, and titers of other serum autoantibodies had also decreased. In May 2001, although the patient remained positive for MPO-ANCA at a low titer, she remained well, with no recurrence of GN.

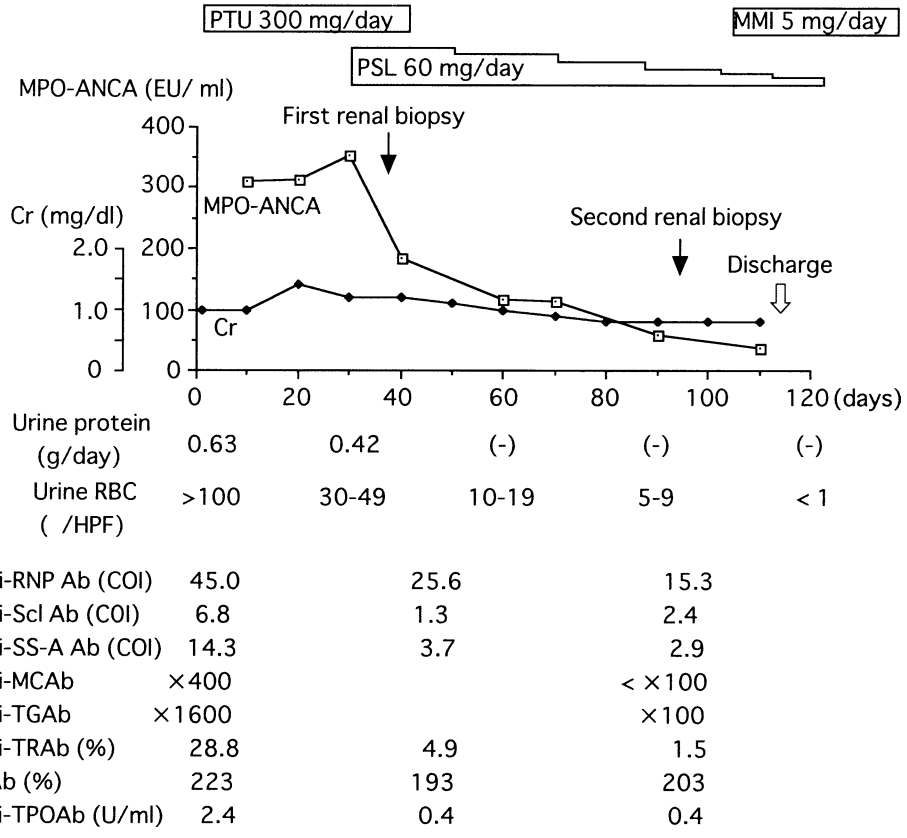

Fig. 2. Effects of cessation of PTU therapy and prednisolone treatment on urinalysis results, and titers of ANCA and other autoantibodies. *PSL*, prednisolone; *MPO-ANCA*, myeloperoxidase-antineutrophil cytoplasmic antibody; *PTU*, propylthiouracil; *MMI*, methimazole; *Cr*, creatinine; *MCAb*, microsomal antibody; *TGAb*, thyroglobulin antibody; *TRAb*, thyroid-stimulating hormone (TSH)-receptor antibody; *TSAb*, thyroid-stimulating antibody; *TPOAb*, thyroperoxidase antibody

Discussion

There have been more than 30 reported cases of ANCA-associated crescentic GN and vasculitis in association with antithyroid medication. Compared with the previous cases, our patient had notable features that suggested her high susceptibility to autoimmune diseases: she had a history of PBC, and most thyroid-associated autoantibodies, together with ANA, were present at the time of diagnosis of Graves' disease. The absence of antimitochondrial Ab at the time of diagnosis might be an effect of ursodeoxycholic acid, which she had taken for PBC.[5–8] We cannot totally deny the possibility that ANCA had been present before the start of the PTU therapy. However, the observations that hematoproteinuria, recurring fever, and other symptoms appeared after starting the PTU therapy, and its cessation resulted in a decreased titer of ANCA together with an improvement in clinical symptoms, indicate that PTU triggered the production of ANCA. We certainly have to consider the effect of steroidal therapy on the reduction of serum ANCA titers, but the reduction was so easily accomplished and so rapid that we thought the cessation of PTU therapy was essential in order to improve the ANCA and ANCA-related symptoms.

The pathogenesis of PTU-induced ANCA-associated crescentic GN and vasculitis has not been defined. First, the mechanism by which PTU induces the production of ANCA remains unclear. However, PTU has been shown to inactivate peroxidase,[9] which indicates that PTU may participate in ANCA production by altering the structure of peroxidase. Second, positivity for PR3- or MPO-ANCA itself is not always associated with the development of vasculitis or crescentic GN, and little is known about the factors that induce these diseases. However, since patients with PTU-induced ANCA-associated vasculitis tend to have a higher titer of ANCA than those without vasculitis,[10] a high titer of ANCA seems to be necessary in the induction of vasculitis and crescentic GN. Furthermore, several in vitro studies have shown that genetic factors play an important role in the development of these diseases.[3,11–14] (1) PR3-ANCA interferes with the inactivation of PR3 by α1-antitrypsin, a natural inhibitor of PR3. It is suggested that the failure to inactivate PR3 may contribute to the inflammatory process. The phenotypic expression of α1-antitrypsin is polymorphic, and it has been reported that phenotypes showing a deficiency in proteinase inhibitor activity were enhanced in PR3-ANCA-positive patients with vasculitis.[12,13] (2) The priming of neutrophils by tumor necrosis factor (TNF)-α results in the expression of MPO and PR3 on the cell membrane, and the activation of neutrophils by ANCA.[15] Considering these results, the capacity for TNF-α production, which is genetically determined,[3] may be a factor in the development of these diseases. (3) Fc binding, as well as F(ab) binding, is involved in the activation of neutrophils. It has been reported that polymorphisms of FcγII receptors also contribute to the activation of neutrophils.[14] Although we did not analyze the pheno-

typic expression of α1-antitrypsin, FcγII receptor, and cytokine levels in our patient, these and other genetic factors may have contributed to her predisposition to autoimmunity.

Susceptibility to an autoimmune disease is influenced by genes within the HLA complex. Although disease-associated HLA has varied in different studies,[3,4,16] our patient carried certain HLA haplotypes that had been reported to be related to ANCA-associated vasculitis and crescentic GN. Our patient carried a DR9 haplotype, which has been reported to be related to MPO-ANCA-associated GN in the Japanese population.[4] Moreover, it is noteworthy that our patient also carried the DR4 haplotype, which has been reported to be associated with a high rate of TNF-α synthesis.[3] Taking those factors together, our patient clearly had certain serological types of HLA which are related to MPO-ANCA-associated GN.

In conclusion, our patient had a genetic predisposition to autoimmunity. Consequently, PTU induced the production of ANCA and the subsequent development of crescentic GN. Further studies to clarify common genetic factors underlying PTU-induced ANCA-associated GN will help us predict the development of ANCA-associated diseases in patients undergoing PTU therapy.

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