Mod Rheumatol (2005) 15:294–296
DOI 10.1007/s10165-005-0408-8

CASE REPORT

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The onset of Graves' disease during the clinical course of myeloperoxidase antineutrophil cytoplasmic antibody (MPO-ANCA)-associated glomerulonephritis

Received: March 8, 2005 / Accepted: May 23, 2005

Abstract A 47-year old man presented with atrial fibrillation, weight loss, hand tremor, and hyperperspiration concurrent with the reactivation of the disease activity of myeloperoxidase antineutrophil cytoplasmic antibody (MPO-ANCA)-associated glomerulonephritis. Laboratory findings indicated that the hyperthyroidism had already existed when glomerulonephritis was detected, and Graves' disease became evident while decreasing the dose of prednisolone. Although the levels of thyroid-stimulating hormone receptor antibody, antithyroid peroxidase antibody, and myeloperoxidase antibody increased, both disease activities were suppressed by increasing the dose of prednisolone. This case indicates that MPO-ANCA-associated glomerulonephritis and Graves' disease may share a common pathogenesis.

Key words Antithyroid peroxidase (TPO) antibody · Crescentic glomerulonephritis (GN) · Graves' disease · Myeloperoxidase antineutrophil cytoplasmic antibody (MPO-ANCA)

Introduction

Graves' disease is recognized as an autoimmune disease and highly complicates other rheumatic diseases, such as rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis, and systemic sclerosis.[1–3] Moreover, myeloperoxidase antineutrophil cytoplasmic antibody (MPO-ANCA)-associated vasculitis often appears as a side effect of antithyroid treatment with propylthiouracil (PTU) for Graves' disease. A withdrawal of the drug with or without immunosuppressive therapy ameliorates the organ damage. These clinical signs indicate that etiologic and genetic factors may be involved in the PTU-induced MPO-ANCA production and that PTU is one of the immunomodulators in the pathogenesis of vasculitis.[4] However, an important question remains unanswered of whether the reverse is also true, i.e., does Graves' disease itself possess the potent mechanism leading to MPO-ANCA vasculitis? We herein report a case of a patient who, while being treated with steroids for MPO-ANCA-associated glomerulonephritis (GN), was diagnosed with Graves' disease.

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Case report

A 47-year-old man was found to have microhematuria at the time of his medical health check. He had a history of physical fatigue over the previous 6 months. Thyroidectomy had been performed on his elder brother because of uncontrollable Graves' disease. His elder sister had also received antithyroid medication for Graves' disease. Both of them are currently being maintained in a healthy state and they have never suffered from other autoimmune diseases such as MPO-ANCA-associated vasculitis. The patient's first laboratory findings revealed a mild renal insufficiency [1.5 mg/dl serum creatinine (Cr), 117 mg/dl urinary protein, >100 counts/high-power field of red blood cells (RBCs) in urinary sediment], mild anemia [406×10^4/μl RBCs, 11.5 g/dl hemoglobin (Hb)], and mild inflammation [0.4 mg/dl C-reactive protein (CRP)]. His blood was negative for antinuclear antibodies, cryoglobulin, and viral markers for hepatitis B and C. After a month of observation during which no treatment was given, his renal function (1.8 mg/dl serum Cr) and anemia (370×10^4/μl RBCs, 10.9 g/dl Hb) had progressively worsened with an increase of inflammatory

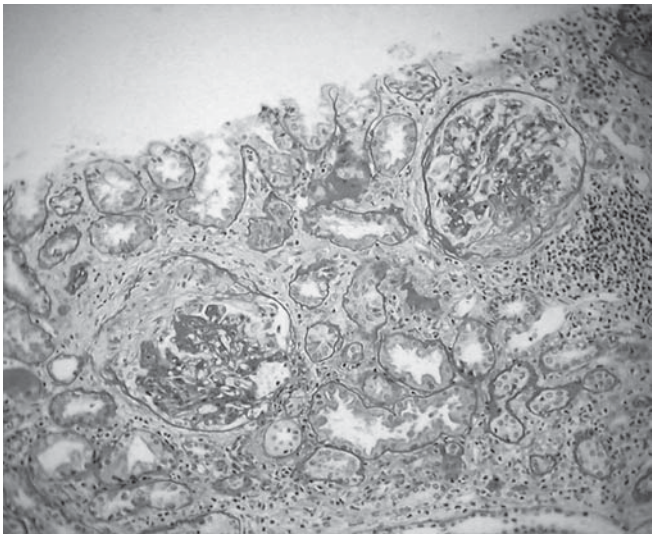

Fig. 1. Renal biopsy specimen. Fibrocellular crescents were noted in all seven glomeruli examined. Ruptured glomerular capillary tuft and sclerotic damage are shown. The infiltrated interstitium with inflammatory cells surrounded the crescentic glomeruli (PAS stain, × 200)

signs [0.7 mg/dl CRP, 66 mm/h erythrocyte sedimentation rate (ESR)]. Renal biopsy was performed and the histology (Fig. 1) showed crescentic GN with interstitial and vascular invasion of inflammatory cells. All of seven glomeruli had a fibrocellular crescent. Immunoglobulins (IgG, IgA, and IgM), C3 breakdown products (C3c, C3d, and C4d), C1q, and fibrinogen were not detectable by immunofluorescence histochemistry. Based on the result of MPO-ANCA measurement of 309 EU (by enzyme-linked immunosorbent assay, normal range: <10 EU), he was diagnosed with MPO-ANCA-associated crescentic GN. Treatment with steroid therapy including two cycles of steroid pulse therapy (methylprednisolone 1000 mg/day × 3 days) was begun (Fig. 2). Urinalysis and creatinine clearance showed a good response to the therapy along with an improvement of the level of MPO-ANCA, ESR, and CRP.

The dose of prednisolone was gradually tapered from 40 to 10 mg/day. Ten months later, the level of total cholesterol (TC), albumin, and body weight (BW) had gradually decreased and atrial fibrillation was detected for the first time. Mild tremors in both hands and mild hyperperspiration also appeared. Laboratory findings indicated hyperthyroidism [5.6 μg/dl free T4, <0.005 μIU/ml thyroid-stimulating hormone (TSH)] with worsening of the levels of MPO-ANCA, ESR, and CRP, which in turn signified the disease activity

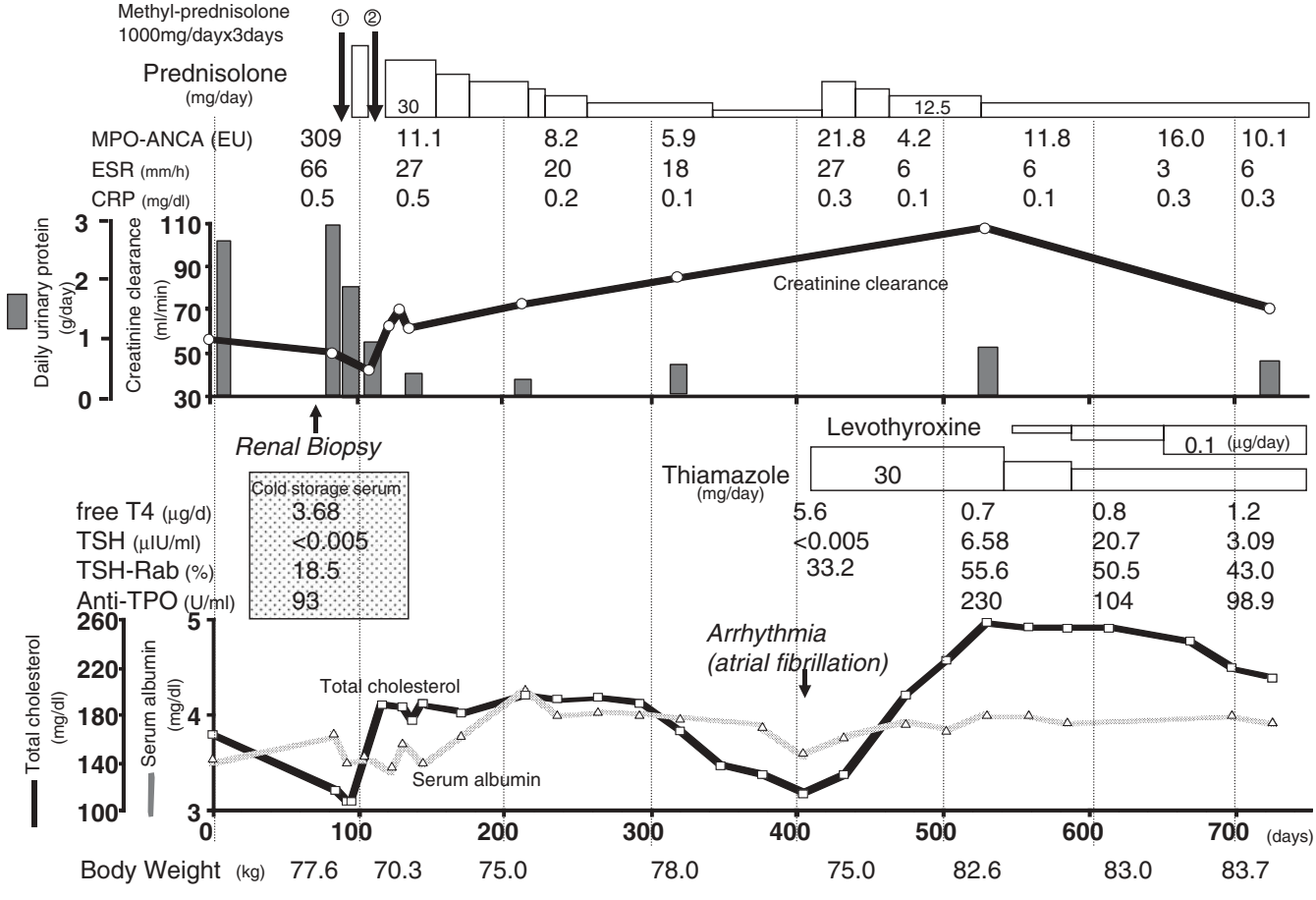

Fig. 2. Clinical course. *MPO-ANCA*, myeloperoxidase antineutrophil cytoplasmic antibody; *ESR*, erythrocyte sedimentation rate; *CRP*, C-reactive protein; *TSH*, thyroid-stimulating hormone; *TSH-Rab*, TSH receptor antibody; *TPO*, thyroid peroxidase

of MPO-ANCA-associated crescentic GN. Because the level of TSH receptor antibody (TSH-Rab) was 33.2% (normal range: <15%), he was diagnosed with Graves' disease. From the start of antithyroid therapy with thiamazole (30 mg/day) and upping the dose of PSL, a gradual increase of TC, albumin, and BW were noted. In addition, the titers of TSH-Rab and antithyroid peroxidase (TPO) antibody decreased with the improving levels of MPO-ANCA, ESR, and CRP.

The patient serum, obtained at the time of renal biopsy and which had been stored frozen, was analyzed after obtaining informed consent. It showed that he was in a hyperthyroid state at that time before the initiation of steroid treatment. The assay results were 3.68 μg/dl free T4, <0.005 μIU/ml TSH, 18.5% TSH-Rab, and 93 U/ml anti-TPO antibody.

Discussion

To our knowledge, this is the first case of Graves' disease that developed during the clinical course of MPO-ANCA-associated crescentic GN. In our case, the patient had hyperthyroidism at the time of occurrence of MPO-ANCA-associated GN but had not shown the symptoms of Grave's disease. While diminishing doses of steroid therapy for his MPO-ANCA-associated GN, evidence of Graves' disease was detected while the dose of prednisolone was being tapered. At the same time, there was a revival of the disease activity of MPO-ANCA-associated GN. It seems that the titer of anti-MPO antibody ran parallel with of anti-TPO antibody. Regardless of 42% homology between the amino sequences of TPO and MPO,[5,6] a recent report showed that the absence of cross-reactivity to MPO of anti-TPO antibody.[7] Also, Gumà et al. reported that 13% of patients with Graves' disease showed positive MPO-ANCA before medical treatment.[8] Clinically, weight loss often appears in patients with MPO-ANCA-associated vasculitis but no clear explanation for this exhaustive mechanism is known. Possibly, hyperthyroidism may lurk behind the pathogenesis of MPO-ANCA-associated vasculitis. A genetic mechanism is implicated, considering that the patient's sister and brother both suffered from Graves' disease though not from vasculitis.

Graves' disease has the potential to produce autoantibodies because the $CD5^+$ B lymphocytes are significantly increased in a polyclonal manner.[9,10] Our case demonstrated the polyclonal activation of B cells, which lead to the production of several types of organ-specific autoantibodies (anti-TPO antibody, anti TSH-Rab) and a non-organ-specific autoantibody (anti-MPO antibody) at one time. Harper et al. concluded that the altered immune environment associated with autoimmune thyroid disease is not sufficient to develop ANCA but treatment with PTU is important in promoting ANCA development.[4] However, our case had never been prescribed such a thionamide previously. Although we could not clarify whether these two diseases might be complicated accidentally, it appears that the pathogenesis of Graves' disease itself has a tendency to develop MPO-ANCA-associated vasculitis without sPTU.

In summary, we report a case of Graves' disease, which was detected during the decline of MPO-ANCA-associated GN. Based on the polyclonal activation of lymphocytes, this case might present two types of autoimmune diseases, MPO-ANCA-associated GN and Graves' disease, at one time.

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