Tumor Necrosis Factor-α Inhibitor-induced Antiglomerular Basement Membrane Antibody Disease in a Patient with Rheumatoid Arthritis

To the Editor:

Tumor necrosis factor (TNF)–targeted therapy is widely used for various rheumatic diseases. However, severe adverse effects have been reported, with a number of studies reporting the development of vasculitis associated with anti-TNF agents[1,2,3]. This is the first report, to our knowledge, of a patient with rheumatoid arthritis (RA) who developed antiglomerular basement membrane (anti-GBM) antibody disease during treatment with adalimumab, a fully human immunoglobulin G1 monoclonal antibody against TNF-α.

A 69-year-old woman was diagnosed with RA based on the criteria of the American College of Rheumatology/European League Against Rheumatism (2010) at the age of 68 years because she presented with symmetrical small-joint arthritis and was positive for anticitrullinated protein antibodies (ACPA)[4]. Treatment with methotrexate, bucillamine, and prednisolone was started, but was stopped 5 months later because interstitial lung disease was detected, after which adalimumab was initiated (40 mg biweekly). There were no findings of renal dysfunction, proteinuria/hematuria, or rheumatoid vasculitis before adalimumab therapy. After 4 months of adalimumab administration, however, she was hospitalized because of severe malaise. Her creatinine level was elevated, and urinalysis showed microscopic hematuria and cellular casts. She was then transferred to our hospital on suspicion of rapidly progressive glomerulonephritis (RPGN).

On admission, she presented with bilateral leg edema and purpura. The laboratory examination findings were white blood cells 16,400/μl; hemoglobin 7.8 g/dl; platelet count 16.4 × 10^4/μl; C-reactive protein 240.3 mg/l (normal < 3 mg/l); blood urea nitrogen 64 mg/dl; serum creatinine 400.9 μmol/l; myeloperoxidase antineutrophil cytoplasmic antibody (MPO-ANCA) 368 ELISA units (normal < 20 EU); and anti-GBM antibody 44 EU (normal < 9.9 EU). No proteinase 3-ANCA or antinuclear antibodies were detected. Skin biopsy specimen of the left leg showed leukocytoclastic vasculitis. Although her serum creatinine level continued to rise, we did not perform renal biopsy because of her poor condition. There were no signs of alveolar hemorrhage. We discontinued adalimumab immediately, and introduced intravenous corticosteroid pulse therapy (1 g/day methylprednisolone × 3 days) followed by oral prednisolone (50 mg/day), cyclophosphamide (50 mg/day), and 6 courses of plasmapheresis. Her renal function did not recover and she remained dialysis-dependent.

We speculated that an anti-TNF agent induced the systemic vasculitis, and conducted a time-series analysis of the titers of anti-GBM antibody and MPO-ANCA in preserved sera obtained before and during TNF-targeted therapy. Although there had been no sign of vasculitis, MPO-ANCA was detected before adalimumab administration. We found evidence that MPO-ANCA had become significantly elevated and the anti-GBM antibody had appeared after adalimumab administration (Figure 1). Severe malaise and RPGN had occurred after the appearance of anti-GBM antibody.

TNF blockade appears to be associated with the development of vasculitis. Saint Marcoux and De Bandt reported the results of a French nationwide survey and identified 39 cases with vasculitis caused by TNF-α antagonists[1]. Ramos-Casals, *et al* reviewed 379 cases of anti-TNF agent-induced autoimmune diseases and identified 118 patients with vasculitis, most of whom showed cutaneous leukocytoclastic vasculitis, and 11 (9.3 %) were positive for ANCA[2]. However, we have found no reports of the development of anti-GBM antibody disease during treatment with anti-TNF agents.

The target antigen for anti-GBM antibody is the α-3 chain of type IV collagen [α3 (IV) NC1], and anti-GBM antibody is undoubtedly pathogenic. A number have dealt with patients with anti-GBM antibody and MPO-ANCA coexisting[5]. It has also been reported that up to one-third of patients with circulating anti-GBM antibody are also positive for ANCA, mainly with specificity for MPO, and that 7.5% of those with ANCA possess anti-GBM antibody[5,6]. The relatively high incidence of such dual positivity suggests a pathogenic link, but that remains to be verified. It is tempting to speculate that ANCA-associated mechanisms may lead to exposure of the immunologic epitopes embedded in the GBM. Some studies reporting that positivity for ANCA was followed by positivity for

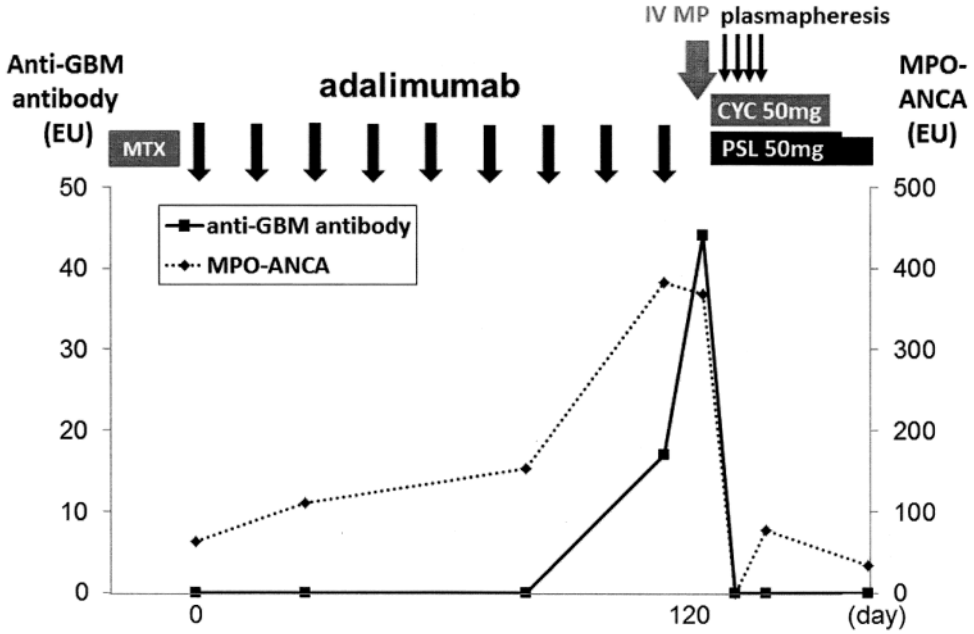

Figure 1. Time course for antiglomerular basement membrane (anti-GBM) antibody and myeloperoxidase antineutrophil cytoplasmic antibody (MPO-ANCA) before and after adalimumab administration. MTX: methotrexate; IV MP: intravenous methylprednisolone; CYC: cyclophosphamide; PSL: prednisolone; EU: ELISA units.

anti-GBM antibody support this hypothesis, but others report the opposite sequence[7,8].

While it remains unclear which is the primary contributor to vasculitis in patients with both ANCA and anti-GBM antibody, several reports suggest that the characteristics of these patients are more like those of anti-GBM antibody disease than of ANCA-associated vasculitis[5]. Although anti-TNF therapy-induced elevation of MPO-ANCA may have triggered the production of anti-GBM antibody in our case, the principal contributor to the development of renal damage could well have been anti-GBM antibodies.

We report the first case, to our knowledge, of anti-TNF agent-induced anti-GBM antibody disease in a patient with RA. A careful clinical and immunological evaluation, including baseline testing for ANCA, should thus be performed before anti-TNF therapy is initiated.

KEISUKE NISHIMURA, MD, Graduate Student, Department of Clinical Pathology and Immunology; JUN SAEGUSA, MD, PhD, Assistant Professor, Department of Clinical Pathology and Immunology and Department of Evidence-based Laboratory Medicine; SEIJI KAWANO, MD, PhD, Lecturer; AKIO MORINOBU, MD, PhD, Associate Professor, Department of Clinical Pathology and Immunology, Kobe University Graduate School of Medicine, Kobe, Japan. Address correspondence to Dr. J. Saegusa, Department of Clinical Pathology and Immunology, Kobe University Graduate School of Medicine, 7-5-1 Kusunoki-cho, Chuo-ku, Kobe 650-0017, Japan. E-mail: jsaegusa@med.kobe-u.ac.jp

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J Rheumatol 2012;39:9; doi:10.3899/jrheum.120325