The increase of antiglomerular basement membrane antibody following pauci-immune-type crescentic glomerulonephritis

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Abstract
A 50-year-old woman was admitted because of high fever and fatigue. Proteinuria, hematuria, and elevated BUN (47.8 mg/dl) and creatinine (3.4 mg/dl) suggested rapidly progressive glomerulonephritis. The serological study revealed all negative results for rheumatoid factor, antinuclear antibody, serum cryoglobulins, MPO-ANCA, PR3-ANCA, and anti-streptolysin O. Antiglomerular basement membrane (GBM) antibody, as assessed by ELISA, was 11 EU (normal, <10). Kidney biopsy on the eighth hospital day demonstrated pauci-immune-type crescentic glomerulonephritis without ANCA. Methylprednisolone pulse therapy (500 mg/day, 3 days) and 45 mg/day prednisolone orally were started. At 3 weeks after kidney biopsy, the anti-GBM antibody value increased from 11 EU/ml to 116 EU/ml, and MPO and PR3-ANCA were still negative. HLA type was DR8 and DR 15(2), with a genotype of HLA-DRB1*08021 and HLA-DRB1*15011. The present case suggests that HLA-DR15 plays an important role on antibody production against alpha 3(IV) NC1 autoantigen after severe nephritis or tissue damage.

Key words Anti-GBM antibody · HLA-DR 15 · Pauci-immune-type crescentic glomerulonephritis

Introduction
Crescentic glomerulonephritis is divided into four types according to their causative factors: antiglomerular basement membrane (GBM) antibody, immune complex, pauci-immune with antineutrophil cytoplasmic antibody (ANCA), and pauci-immune without ANCA. For the anti-GBM antibody type, there are two clinical phenotypes, one limited to the glomeruli, and the other, known as Goodpasture syndrome, involving both glomerulonephritis and pulmonary hemorrhage. Recently, a simple enzyme-linked immunosorbent assay (ELISA)-based system has been developed to detect circulating anti-GBM antibody recognizing alpha 3 type IV collagen NC1-domain antigen epitope [alpha 3(IV) NC1 domain antigen]. As a clinical problem, there are some patients who have both anti-GBM antibody and ANCA.

We report herein an adult patient with pauci-immune without ANCA-type crescentic glomerulonephritis who developed anti-GBM antibodies while receiving prednisolone, and discuss the possible mechanism underlying anti-GBM antibody production.

Case report
A 50-year-old woman was admitted to Aichi Medical University Hospital on April 3, 2003, because of high fever and fatigue. She had been treated with antihypertensive drugs (β-blocker and diuretics) since 1999, and a recent laboratory examination revealed a blood urea nitrogen (BUN) level of 8.9 mg/dl and a serum creatinine level of 0.8 mg/dl. Two weeks before admission to the hospital, she had high fever and diarrhea. She developed anorexia and easy fatigue even while receiving fosfomycin and levofloxacin.

On admission, her vital statistics were as follows: body temperature, 38.1°C; pulse rate, 84 beats/min; respiratory rate, 16 breaths/min; and blood pressure, 124/72 mmHg. A physical examination showed anemic conjunctiva and bilateral knock pain on the costovertebral region of her back. Cardiopulmonary, abdominal, and neurological examinations were normal.

Urinary protein was 2+, occult blood reaction was 3+ for dipsticks, and the urine sediment showed 10–15 red blood cells per high power field and 31–50 white blood cells (WBC) per high power field with hyaline cast, granular cast,
Blood counts were as follows: erythrocytes, $324 \times 10^4/\mu l$, hemoglobin, 10.2 g/dl; hematocrit, 30.4%; leukocyte count, 10,100/µl (neutrophils 82%, lymphocytes 12%, monocytes 5%); and platelets, $54.3 \times 10^4/\mu l$.

Blood chemistry values were as follows: serum total protein, 8.4 g/dl; albumin, 3.8 g/dl; blood urea nitrogen, 47.8 mg/dl; creatinine, 3.4 mg/dl; uric acid, 7.5 mg/dl; total bilirubin, 0.5 mg/dl; aspartate aminotransferase, 37 IU/l; alanine aminotransferase 39 IU/l; lactic dehydrogenase, 267 IU/l; alkaline phosphatase, 676 IU/l; and total cholesterol, 138 mg/dl.

Immunological data were as follows: C-reactive protein, 23.4 mg/dl; IgG, 1174 mg/dl (normal range, 880–1800); IgA, 282 mg/dl (normal range, 52–270); IgM, 73 mg/dl (normal range, 17–40); C₃, 220 mg/dl (normal range, 84–151); C₄, 42 mg/dl (normal range, 17–40); CH₅₀, 63 U/ml (normal range, 30–40). The patient was negative for rheumatoid factor, antinuclear antibody, serum cryoglobulins, MPO-ANCA, PR3-ANCA, and p- and c-ANCA by immunofluorescent study, and antistreptolysin O. Anti-GBM antibody, as assessed by ELISA, was 11 EU (normal, <10).

Cultures from arterial and venous blood were negative in all three trials, and urinary bacterial cultures were negative. Results of chest radiography and electrocardiogram were within normal limits.

Gallium scintigram demonstrated bilateral kidney uptake (Fig. 1). A kidney biopsy was performed on the eighth hospital day. Light microscopic examination showed that 2 of 20 glomeruli were globally sclerosed, and the remaining 18 glomeruli showed circumferential cellular crescents with necrotizing lesion. Mononuclear cells had infiltrated into tubules and interstitial tissue with mild degree of interstitial fibrosis (Fig. 2). Immunofluorescence studies revealed no glomerular deposition of linear and granular IgG, IgA, IgM, kappa, lambda, C₃, or C1q, but fibrinogen 2+ was found in the crescentic areas and interstitial tissue (Fig. 3). Unfortunately, we could not evaluate the glomerular changes because the specimen mainly contained tubular damage.

Clinical course (Fig. 4): kidney biopsy on the 8th hospital day revealed pauci-immune-type crescentic glomerulonephritis without ANCA. We started methylprednisolone pulse therapy (500 mg/day, 3 days) and 45 mg/day prednisolone orally. We reexamined the circulating IgG-class anti-GBM antibody level at 3 weeks after kidney biopsy because the initial value was slightly over the limit and the patient showed a worsening serum creatinine level even while on prednisolone therapy. At this point, the anti-GBM antibody value increased from 11 to 116 EU/ml (no elevation of IgA or IgM-class anti-GBM antibodies) and MPO and PR3-ANCA were still negative, leading us to perform two courses of plasma exchange in addition to hemodialysis, and to continue administration of 30 mg/day prednisolone. At discharge (the 78th hospital day), proteinuria and hematuria were 2+, the titer of anti-GBM antibody had decreased to 13 EU/ml, BUN was 60.6 mg/dl, and creatinine was 2.8 mg/dl (see Fig. 4). Three months after discharge, the titer of anti-GBM antibody dropped below 10 EU/ml, BUN was 46.5 mg/dl, and creatinine was 2.3 mg/dl. The patient’s HLA type was DR8 and DR 15(2), with a genotype of HLA-DRB1*08021 and HLA-DRB1*15011.

**Discussion**

The patient shows two unique points, that severe nephritis induces costovertebral spontaneous and knock pain, and...