Development of Anti–Glomerular Basement Membrane Disease After Remission From Perinuclear ANCA-Associated Glomerulonephritis in a Patient With HLA Susceptibility

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A 62-year-old woman presented with acute renal failure, hematuria, proteinuria, and increased C-reactive protein level. She was positive for antineutrophil cytoplasmic antibodies (ANCAs) directed against myeloperoxidase (MPO) and negative for anti–glomerular basement membrane antibody. Kidney biopsy confirmed a diagnosis of pauci-immune crescentic glomerulonephritis with no immunoglobulin G staining. Remission was induced with prednisolone and intravenous cyclophosphamide, followed by maintenance therapy with azathioprine, during which MPO-ANCA results became negative. Nine months after the initial presentation, kidney function rapidly deteriorated again in association with hematuria, proteinuria, and increased C-reactive protein level. A second kidney biopsy again showed crescentic glomerulonephritis; however, on this occasion, direct immunofluorescence showed prominent linear staining of the glomerular basement membrane with immunoglobulin G. Test results were strongly positive for glomerular basement membrane antibody, but remained negative for MPO-ANCA. HLA-DR typing showed HLA-DRB1*15011, an allele strongly associated with anti–glomerular basement membrane disease. To our knowledge, this is the only reported case of 2 distinct forms of crescentic glomerulonephritis characterized by separate autoantibody profiles developing sequentially in a patient with proved HLA susceptibility. We speculate that glomerular damage caused by the initial renal insult resulted in a subsequent autoimmune response to autoantigen presented on the HLA-DR susceptibility allele.

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INDEX WORDS: Anti–glomerular basement membrane antibody (anti-GBM); antineutrophil cytoplasmic antibody (ANCA); glomerulonephritis; HLA.

Rapidly progressive glomerulonephritis (GN) is a clinical syndrome characterized by acute kidney failure caused by glomerular disease associated with crescent formation on kidney biopsy specimens. It usually is caused by 1 of 4 immunopathologic processes: type I, anti–glomerular basement membrane (anti-GBM) or Goodpasture disease; type II, immune complex–mediated disease; type III, pauci-immune disease (typically antineutrophil cytoplasmic antibody [ANCA] associated); and type IV, double-positive disease (features of both type I and type III).[1] We report the first case of a patient who initially presented with type III (ANCA-associated) rapidly progressive GN, but after induction of stable remission, subsequently developed type I (anti-GBM) disease. Each presentation was associated with distinct and characteristic autoantibody profiles and direct immunofluorescence patterns.

CASE REPORT

A 62-year-old Indian woman with a history of hypertension, vitiligo, and osteoporosis presented with dyspnea, anorexia, and vomiting. She was in kidney failure, with the following laboratory values: creatinine, 2.24 mg/dL (198 μmol/L; estimated glomerular filtration rate, 24 mL/min/1.73 m^2 [0.40 mL/s/1.73 m^2]); urea, 23.5 mg/dL (8.39 mmol/L); hemoglobin, 8.0 g/dL (80 g/L); white blood cell count, 14.3 × 10^3/μL (14.3 × 10^9/L), and C-reactive protein (CRP), 240 mg/L. Urinalysis showed protein (3+), blood (3+), and 200 occasionally dysmorphic red blood cells/μL. Urine culture was sterile. Serologic studies showed strongly positive ANCA in a perinuclear pattern on indirect immunofluorescence with myeloperoxidase (MPO) reactivity on enzyme-linked immunosorbent assay (43 U/mL; normal, <10 U/mL). Antinuclear antibodies were positive in a mixed homogeneous (titer, 1:640) and nucleolar pattern (titer, 1:2,560) on indirect immunofluorescence, and anti–double-stranded DNA antibody level was mildly increased (7 IU/mL; normal, 0-5 IU/mL). However,

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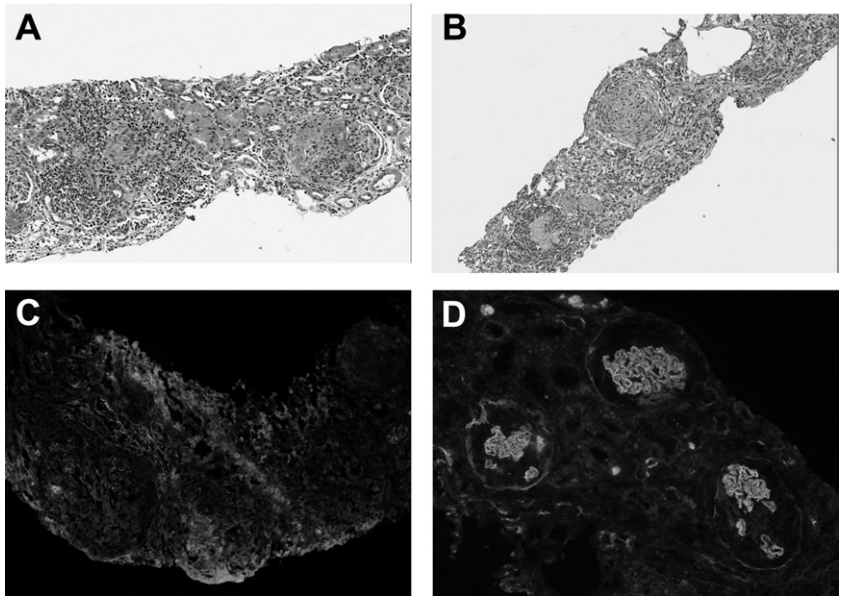

Figure 1. Kidney biopsy findings at (A, C) initial presentation and (B, D) 9 months later. (A, B) Light microscopy shows glomerular crescents and moderate inflammatory cell infiltrates in both kidney biopsy specimens. (Periodic acid–Schiff stain; original magnification, ×20.) (C) Direct immunofluorescence examination of frozen sections showed no immunoglobulin G (IgG) deposition, but intense linear IgG deposition on the glomerular basement membrane 9 months later. (Original magnification, [C] ×10; [D] ×20.)

antibodies to extractable nuclear antigens and GBM were negative. A computed tomographic scan of the thorax showed minor areas of atelectasis at the lung bases and moderate bilateral pleural effusions, but no pulmonary infiltrates. Pulmonary function test results were unremarkable.

A kidney biopsy was performed and showed 28 glomeruli, none of which was sclerosed (Fig 1A). Eighteen glomeruli showed fibrinoid necrosis, most of which contained a combination of cellular and fibrocellular crescents. There was moderate mixed inflammatory cell infiltrate of the interstitium with no granulomas seen. One large muscular artery showed fibrinoid necrosis bordered by a rim of inflammatory cells consistent with vasculitis. Sections were stained with antibodies against immunoglobulin G (IgG), IgA, IgM, C3, C1q, fibrinogen, and albumin; the crescents stained with fibrinogen, but there were no significant immune deposits within glomeruli (Fig 1C). A diagnosis of ANCA-associated crescentic GN was made.

The patient was treated with 3 doses of intravenous methylprednisolone (500 mg/d) followed by oral prednisolone (1 mg/kg/d initially, followed by slow tapering) and monthly intravenous cyclophosphamide (750 mg/infusion). By 3 months, she had achieved stable remission with creatinine levels decreasing to 1.35 mg/dL (119 μmol/L; estimated glomerular filtration rate, 42 mL/min/1.73 m^2 [0.70 mL/s/1.73 m^2]), normalization of CRP level (7 mg/L), and no detectable MPO-ANCA (Fig 2). Therapy was converted from intravenous cyclophosphamide to oral azathioprine (2 mg/kg/d), and prednisolone gradually was weaned to a maintenance dose of 5 mg/d.

Nine months after the initial diagnosis, the patient presented a second time to a peripheral hospital with fever, dry cough, and macroscopic hematuria. Physical examination showed temperature of 38.9°C, moderate lower extremity edema, and bibasal pulmonary crepitations. Serum creatinine level had increased to 2.79 mg/dL (247 μmol/L; estimated glomerular filtration rate, 18 mL/min/1.73 m^2 [0.30 mL/s/1.73 m^2]), and CRP level, to 238 mg/L. However, MPO-ANCA results remained negative. Urinalysis showed a trace of protein, trace of leukocytes, and blood (3+), and she was treated initially for a presumed urinary tract infection. The urine culture subsequently showed no growth. She rapidly progressed to anuric acute kidney failure with creatinine level increasing to 12.45 mg/dL (1,101 μmol/L; estimated glomerular filtration rate, 3 mL/min/1.73 m^2 [0.05

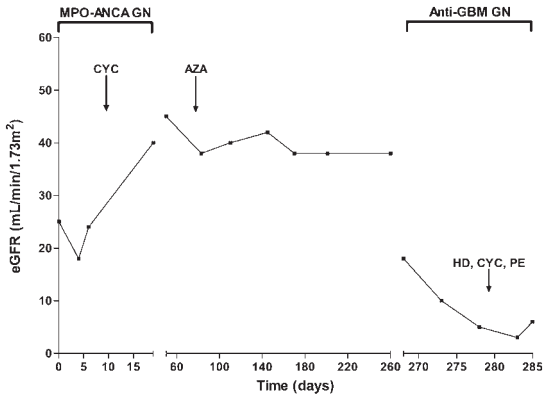

Figure 2. Clinical progress of the patient. The patient's first presentation was with myeloperoxidase-directed antineutrophil cytoplasmic antibody glomerulonephritis (MPO-ANCA GN) that responded to induction therapy with corticosteroids and monthly intravenous cyclophosphamide (CYC; × 3). She remained in stable clinical remission for several months on azathioprine (AZA) therapy. The second presentation was with anti–glomerular basement membrane (anti-GBM) GN. Despite treatment with corticosteroids, oral CYC, and plasma exchange (PE), she developed anuric dialysis-dependent kidney failure. Abbreviations: eGFR, estimated glomerular filtration rate; HD, hemodialysis.