CASE REPORTS

Recurrent Goodpasture's Disease Secondary to a Monoclonal IgA1-κ Antibody Autoreactive With the α1/α2 Chains of Type IV Collagen

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• **Goodpasture's disease is characterized by crescentic glomerulonephritis and lung hemorrhage in the presence of anti–glomerular basement membrane (anti-GBM) antibodies. This disease usually is mediated by IgG autoantibodies directed against the noncollagenous domain of the α3(IV) collagen chain, the Goodpasture autoantigen. In rare cases, anti-GBM antibodies of IgA or IgM class are involved, but their specificity has not been determined, and their target antigen remains unknown. The authors present the case of a 62-year-old man with anti-GBM disease mediated by a monoclonal IgA-κ antibody, which progressed to end-stage renal disease despite intensive immunosuppression. The patient underwent living-related kidney transplantation, but lung hemorrhage and crescentic glomerulonephritis recurred, causing the loss of the allograft 2 years later. Indirect immunofluorescence found the presence of circulating IgA antibodies reactive with a basement membrane component, identified by enzyme-linked immunoabsorbent assay and Western blot as the α1/α2(IV) collagen chains. Sensitivity to digestion with collagenase indicated that IgA bound to epitopes located in the collagenous domain. This is the first case of recurrent Goodpasture's disease secondary to an autoreactive IgA antibody. The specificity of an IgA antibody implicated in the pathogenesis of anti-GBM disease has been investigated for the first time, identifying the α1/α2(IV) collagen chains as a novel target for nephritogenic antibodies. *Am J Kidney Dis* 45:397–406.**

INDEX WORDS: Goodpasture's disease; anti–glomerular basement membrane (GBM) disease; paraproteinemia; IgA-κ antibodies; crescentic glomerulonephritis; pulmonary hemorrhage; kidney transplantation; α1/α2 chains of type IV collagen.

GOODPASTURE'S DISEASE is an autoimmune disease characterized by rapidly progressive crescentic glomerulonephritis associated with pulmonary hemorrhage in the presence of circulating and/or organ-bound anti–glomerular basement membrane (anti-GBM) antibodies.[1] The relative involvement of kidneys and lungs varies among patients, with a spectrum of clinical presentations ranging from isolated kidney anti-GBM disease without overt pulmonary involvement in about 35% of patients, to pulmonary hemorrhage without glomerulonephritis in a small number (<5%) of cases.[2,3] Smooth linear deposits of anti-GBM antibodies identified by immunofluorescence examination of kidney biopsies are a hallmark of the disease, and serum circulating anti-GBM antibodies can be seen using specific solid-phase radioimmunoassay or enzyme-linked immunoassay.

Although relatively rare, anti-GBM disease is a paradigm for antibody-mediated glomerular injury, because the autoantibodies and their target autoantigen have been extensively characterized.[4] The autoantibodies recognize 2 major conformational epitopes within the noncollagenous (NC1) domain of the α3(IV) collagen chain, which is present in the GBM and the alveolar basement membrane.[5-7] In general, anti-GBM autoantibodies are restricted to IgG subclasses, usually IgG1 and IgG4.[8,9] Rarely, anti-GBM disease is mediated by IgA antibodies.[10-14] The specificity of anti-GBM antibodies of IgA class has not been determined, and it is not known whether they target the same "Goodpasture antigen" recognized by IgG anti-GBM antibodies.

We have previously reported an unusual case of Goodpasture disease mediated by a monoclonal IgA-κ antibody, which, albeit deposited along the GBM and other renal basement membrane,

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did not react with the α3(IV)NC1 domain. Deterioration of renal function in this patient prompted preemptive related-donor kidney transplantation. However, the persistence of the circulating IgA monoclonal antibody and its binding to the renal allograft GBM led to recurrence of Goodpasture's disease and eventual loss of the allograft. The monoclonal antibody was most likely secondary to a plasma cell dyscrasia that had not been eliminated before transplantation. Recurrence of anti-GBM disease in the kidney allograft is very rare[15] and has not been described previously for an anti-GBM antibody of IgA class. Analysis of the patient's serum by enzyme-linked immunosorbent assay (ELISA) and immunoblotting determined that the autoreactive circulating IgA antibody recognized epitopes located in the collagenous domain of the α1/α2(IV) collagen network. The specificity of an IgA antibody implicated in the pathogenesis of anti-GBM disease has been established for the first time, identifying the α1/α2(IV) collagen network as a distinct new target of nephritogenic antibodies.

CASE REPORT

A 62-year-old man with end-stage renal disease (ESRD) secondary to Goodpasture's disease underwent living donor–related kidney transplantation in 2001. The patient had initially presented in 1996 with a history of multiple episodes of pulmonary hemorrhage. Extensive evaluation found a monoclonal IgA-κ paraprotein in the serum. Smooth linear GBM deposits of IgA and κ light chain were also seen on immunofluorescence staining in the renal biopsy. The diagnosis of IgA-κ–mediated Goodpasture's disease was established. Details of the case were described previously by our group.[14] The patient was treated with prednisone (60 mg/d) and cyclophosphamide (150 mg/d) together with weekly plasma exchanges for 6 weeks with resolution of his symptoms. Since the original report, the patient had 3 relapses of pulmonary hemorrhage. Several serum protein electrophoreses showed the level of IgA protein had remained constant, which made the correlation between the IgA levels and disease exacerbation difficult to establish. Eventually, the patient had progressive renal failure and received a preemptive living-related donor kidney transplant in February 2001.

At the time of transplantation, the patient was in clinical remission, although the monoclonal IgA-κ spike was still present. The immunosuppression protocol consisted of antithymocyte globulin (Thymoglobulin) induction followed by sirolimus, mycophenolate mofetil, and prednisone. The posttransplantation course was uneventful with no rejection episodes. At 3 months, a protocol allograft biopsy showed no evidence of rejection or glomerular lesion, although immunofluorescence staining showed a diffuse linear deposition of IgA (2+) and κ light chain in the GBM and, to a lesser extent, in the tubular basement membranes. No deposition of IgG, IgM, $C1_q$, C3, or λ light chain was present. Because his renal function was stable (serum creatinine, 1.7 mg/dL [150 μmol/L]) and he had a normal urinalysis, no changes were made, and it was recommended to the patient to continue on his current immunosuppressive regimen.

Nine months after kidney transplantation (December 2001), the patient returned for medical attention with a history suggestive of a persistent viral upper respiratory infection for 2 months. Blood pressure was 130/90 mm Hg on single use of Benazepril, 10 mg orally every day. Serum creatinine was 1.6 mg/dL (141 μmol/L). Urinalysis showed 4 to 10 red blood cells (RBCs) per high-power field, greater than 25% dysmorphic, with a predictive proteinuria of 536 mg/24 h. Other laboratory results were unremarkable. Chest computerized tomography (CT) showed bilateral diffuse ground glass changes, predominantly in the upper lungs. Bronchoscopic examination had findings consistent with hemosiderosis and pulmonary scarring but no evidence of active lung hemorrhage, infections, or neoplasia. Follow-up was recommended. A new protocol allograft biopsy carried out 12 months after kidney transplantation showed a small cellular crescent in 1 of 15 glomeruli. The remaining glomeruli were unremarkable. Tubules and interstitium presented no significant inflammation apart from focal minimal fibrosis. Immunofluorescent histology found a bright capillary wall staining for IgA (3+). There was focal vascular staining for C3 (1 to 2+), tubular epithelial staining for albumin (1+), and focal interstitium staining for fibrinogen (trace). No acute rejection was identified. Serum creatinine was 1.5 mg/dL (133 μmol/L). Urinalysis showed greater than 100 RBCs per high-power field with occasional RBC casts. Proteinuria had increased to 2 g/24 h. A bone marrow aspirate and biopsy were performed and showed a slightly hypocellular marrow (25% cellularity), considered to be the result of prolonged exposure to cyclophosphamide. Plasma cells were slightly increased (5% to 10%) and atypical in appearance, and present in foci. Most atypical plasma cells stained negatively for CD20. Plasma cell labeling index was 0.7% (intermediate), with a κ to λ ratio greater than 99:1 (monoclonal κ). Cytogenetic studies found a normal karyotype in 20 of 20 metaphases. Cytogenetic fluorescence in situ hybridization (FISH) studies showed that interphase was normal for all loci studied. Because renal function, based on serum creatinine levels, had remained stable, follow-up was recommended.

Two years after kidney transplantation (February 13, 2003), the patient presented to follow-up with new-onset of hemoptysis and lung nodules on the chest x-ray. Bronchoscopy examination was again negative for malignancy. During the procedure, the patient had chills, fever, and hemoptysis and was admitted to the hospital. On admission, serum creatinine was 2.0 mg/dL (177 μmol/L) and urinalysis showed 11 to 20 RBCs, greater than 25% dysmorphic, and occasional RBC casts. Relapse of Goodpasture's disease was considered, and allograft biopsy was performed. Light microscopy results showed a small segmental scar with a small crescent formation and fibrin deposition with occasional inflammatory cells in 1 of 8 glomeruli. Another glomerulus showed segmental sclerosis with prominent epithelial reaction. The remaining glomeruli were unremarkable. Immunofluorescence showed the characteristic linear