Goodpasture Syndrome Involving Overlap with Wegener’s Granulomatosis and Anti-Glomerular Basement Membrane Disease

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Abstract. A 68-year-old Caucasian woman presented to the hospital with nodular pulmonary infiltrates and acute renal failure. Wegener’s granulomatosis was initially considered to be most likely because of the presence of increased serum levels of c-anti-neutrophil cytoplasmic antibodies (c-ANCA). A consultation through the Internet after a renal biopsy demonstrated crescentic, necrotizing glomerulonephritis and linear deposits of immunoglobulin G (IgG) and complement C3, typical of anti-glomerular basement membrane (GBM) disease. Hemodialysis was instituted; however, the patient suddenly developed a massive cerebral hemorrhage and died before full therapy could take effect. Postmortem analysis of the patient’s sera revealed high titers of IgG against the α3 NC1 domain of type IV collagen. Serologic evidence of both p-ANCA and anti-GBM antibodies are becoming more frequently recognized in the setting of rapidly progressive glomerulonephritis. The patient reported here had the unusual combination of c-ANCA antibodies with anti-GBM disease, and this association raises complex questions regarding the pathogenesis of this type of renal injury. (J Am Soc Nephrol 8: 1795–1800, 1997)

Basement membranes provide supportive underlayment for epithelium in organ tissues. These basal laminae form as a lattice of type IV collagen, laminin, entactin, and proteoglycans. Goodpasture syndrome, a form of anti-glomerular basement membrane (GBM) disease, is characterized by rapidly progressive glomerulonephritis and pulmonary hemorrhage associated with autoantibodies directed to the globular NC1 domains of α3(IV) collagen in selected basement membranes (1,2). Circulating and tissue-bound anti-α3(IV) NC1 antibodies from kidney and lung recognize similar pathogenic epitopes (3,4), and two interaction sites have been identified at each end of the domain (3,4). The presence of these antibodies reflects one pathophysologic component of the disease (1,5–7). The other important immunologic element in anti-GBM disease is the T cell immune response driven by susceptibility genes responsive to the α3(IV) NC1 domain (8,9). Recently, anti-GBM antibodies have been found in the sera of some p-ANCA–positive patients with Wegener’s granulomatosis. Herein, we report this overlap syndrome in a patient with c-ANCA reactivity.

Case History

A 68-year-old female retired schoolteacher presented to an outside hospital with nodular pulmonary infiltrates and rapidly progressive renal failure. Her previous history was remarkable for heavy smoking and chronic obstructive airway disease; 23 years before admission, she underwent upper lobectomy of the right lung for a bacterial infection. Six months before admission, she complained of diffuse but unexplained arthralgias. One month before admission, she developed a new cough and fever. A chest x-ray at that time revealed bilateral pulmonary infiltrates, and Mycobacterium avium was isolated by fine-needle lung aspiration. Her blood urea nitrogen (BUN) and creatinine levels remained normal, her symptoms improved, and the pulmonary infiltrates resolved after treatment with ethambutol and chlor-erythromycin. Three weeks later, the cough and fever recurred in association with increasing shortness of breath and pleuritic chest pain. Her bronchial symptoms worsened despite oral antibiotics, and she was admitted to intensive care at her local hospital with respiratory failure.

Her past medical history included mild chronic sinusitis, right-sided sensory neural hearing loss, supraventricular tachyarrhythmias, mild hypercalcemia, and Schatzki’s ring. All were longstanding and inactive. A review of her symptoms and family history were not informative, although she was said to be allergic to penicillin. There was no known toxin exposure.

On physical examination, she appeared chronically ill, weighing 48.1 kg with a temperature of 99°F, and a blood pressure of 135/55 mmHg. The skin was normal, and there were no mucosal ulceraions. The sinuses were not tender, and her conjunctiva, sclera, and fundoscopic examinations were
normal. Mild, diffuse crackles and wheeze were auscultated throughout both lung fields. The left ventricle was not displaced, the cardiac rhythm was regular, and there were no murmurs, gallops, or rubs. Pulses were present and full in all extremities. The abdomen was without organomegaly, masses, or tenderness; there were no bruits, and the bowel sounds were audible and normal. There was no evidence of arthritis, and the neurologic examination was within normal limits.

Initial laboratory findings included the following values: hemoglobin, 9.3 g/dl; hematocrit, 28.5%; platelets, 710,000/μl; white blood cell count, 19,100/μl (73% neutrophils, 20% lymphocytes, 5% monocytes, and 1% eosinophils); a BUN of 90 mg/dl; creatinine, 13.6 mg/dl; sodium, 143 meq/l; chloride, 109 meq/l; carbon dioxide, 10 mmol/l; potassium, 6.4 meq/l; phosphate, 9 mg/dl; calcium, 8.2 mg/dl; lactate dehydrogenase, 223 U/l; serum aspartate transaminase, 79 U/l; serum alanine transaminase, 89 U/l; albumin, 2.8 g/dl; total bilirubin, 1.2 mg/dl. Red blood cells too numerous to count, 500 mg/dl of protein, and many fine granular casts were found on urinalysis. Chest x-ray and computed axial tomography (CAT) scans revealed new nodular infiltrates in the anterior segment of the left upper lobe, chronic obstructive airway disease, and calcified mediastinal and hilar lymph nodes. A CAT scan of the sinuses was normal. Ultrasound evaluation of the kidneys, liver, and pancreas were unremarkable. Anti-proteinase 3 (c-ANCA) antibody titers were positive at 11 units, whereas anti-myeloperoxidase (p-ANCA) antibody titers were negative. The ANA and hepatitis serologies (A, B, and C) were also negative.

Wegener's granulomatosis was considered to be the most likely clinical diagnosis, and the patient was treated with oxygen, antibiotics, steroids, and hemodialysis. An open renal biopsy revealed extensive necrotizing glomerulonephritis with fibrocellular crescents involving 100% of glomeruli; this was associated with disruption of the glomerular basement membrane and Bowman's capsule (Figure 1A). Large infiltrates of mononuclear cells were present within the interstitium, focal degenerative and atrophic changes were present in the tubular epithelium, and there was evidence of mild arteriosclerosis. Immunofluorescence studies demonstrated intense, diffuse linear staining of IgG along glomerular basement membranes (Figure 1B); there were also occasional, focal, granular glomerular deposits of IgM, C3, and fibrin. When examined by electron microscopy, there was focal collapse of glomerular basement membranes and loss of cells. Extensive effacement of the visceral epithelial foot processes was present. Electron-dense deposits were not visualized. The biopsy findings were consistent with crescentic glomerulonephritis from anti-GBM.

Figure 1. Pathology. (A) Periodic acid-Schiff-stained 5-μM section of the kidney biopsy tissue obtained from the patient. Magnification, ×250. Crescentic glomerulonephritis with interstitial infiltrates is observed in this section. (B) Linear deposits of IgG on the glomerular basement membrane of the patient by direct immunofluorescence, using mouse antihuman IgG antibodies. Occasional tubular basement membrane IgG deposits are also observed. Magnification, ×250.
Table 1. Autoantibodies to glomerular basement membrane and neutrophil cytoplasm in rapidly progressive glomerulonephritis

<table>
<thead>
<tr>
<th>No. of Patients</th>
<th>Anti-GBM-Positive</th>
<th>Anti-GBM-Positive Only</th>
<th>Anti-GBM-And ANCA-Positive</th>
<th>ANCA-Positive</th>
<th>ANCA-Positive with Anti-GBM Antibodies</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>889 RPGN</td>
<td>67 (7.5%)</td>
<td>47 (70%)</td>
<td>20 (30%)</td>
<td>266 (30%)</td>
<td>20 (7.5%)</td>
<td>15 (Jayne et al.)</td>
</tr>
<tr>
<td>23 GPS</td>
<td>23 (100%)</td>
<td>16 (70%)</td>
<td>7 (30%)</td>
<td>1390 (90%)</td>
<td>34 (2.5%)</td>
<td>16 (Weber et al.)</td>
</tr>
<tr>
<td>1550 GN</td>
<td>160 (10%)</td>
<td>126 (79%)</td>
<td>34 (21%)</td>
<td>1390 (90%)</td>
<td>34 (2.5%)</td>
<td>17 (Short et al.)</td>
</tr>
</tbody>
</table>

* RPGN, rapidly progressive glomerulonephritis; GPS, Goodpasture syndrome; GN, glomerulonephritis.

disease. Dialytic therapy was initiated and immunosuppressive therapy was contemplated, but the patient suffered a massive intracerebral hemorrhage and died shortly after her renal biopsy. Several days later, the serum complement levels were reported to be normal, with an anti-GBM antibody titer from an outside laboratory registering 892 units (positive > 20).

Our attention to this patient was first drawn from Internet contact through the Goodpasture home page (http://reh-d.med.upenn.edu:1025/), resulting in further consultation with the family and attending physicians at her outside hospital. A serum sample from the patient was subsequently tested by enzyme-linked immunosorbent assay (ELISA) and Western blot in our laboratory against α3(IV) NC1 collagen extracted from tissue or isolated as recombinant molecule. The assay was positive for anti-GBM antibodies (Figure 2).

Discussion

In addition to anti-GBM disease, several other systemic illnesses may present with Goodpasture syndrome, including Wegener’s granulomatosis, systemic lupus erythematosus, necrotizing vasculitis, and Henoch-Schönlein purpura (10,11). Pneumonia with postinfectious glomerulonephritis may sometimes masquerade as a systemic disease and confound the diagnosis (10,11). In most cases, the serologies and serum complement levels are very helpful in distinguishing these entities (12). Low serum complement levels suggest systemic lupus or postinfectious glomerulonephritis, although patients with right-sided endocarditis may occasionally present with pulmonary infiltrates, hypocomplementemia, and glomerulonephritis (10,11,13). Systemic vasculitis or anti-GBM disease are the most common causes of the normocomplementemic syndrome and, therefore, determination of ANCA and anti-GBM antibody levels are particularly helpful (13). There remains a subgroup of the latter patients that have circulating levels of both ANCA and anti-GBM antibodies (1,14–17). As was the situation in the present case, both the immunofluorescence evaluation of the kidney biopsy and determination of the specificity of the circulating autoantibodies assisted us in arriving at a diagnosis.

Type IV collagen is the major protein in basement membranes such as the GBM (2,18,19). Type IV collagen is composed of six genetically distinct chains termed α1 through α6 (2). The α1 and α2 chains of type IV collagen are present ubiquitously in all basement membranes (2), whereas the α3, α4, α5 and α6 chains have a much more restricted distribution (2). In the kidney, these later chains predominate along the GBM and Bowman’s capsule. The α-chains of type IV collagen can be divided into three domains: the non-collagenous N-terminal 7S domain of variable length, a middle triple helical domain of approximately 1400 amino acid with a characteristic Gly-X-Y motif, and a C-terminal noncollagenous globular domain of approximately 230 amino acids (2,6,20).

Type IV collagen monomer is a triple helical molecule composed of three polypeptide α-chains. With six α-chains of type IV collagen, there are 56 possible combinations of type IV collagen monomer (2,6,20–22). Although some tumors secrete type IV collagen monomers in a 2:1 ratio of α1 and α2 (23,24), firm data regarding the monomer composition for type IV collagen is not available for native human basement membranes. The α3 chain of type IV collagen, the Goodpasture autoantigen, is most abundant in the glomerulus and seminiferous tubule (2,21,25) but is also present in basement membrane from the lung, eye, choroid plexus, and inner ear (6). Basement membranes of placenta, amnion, liver, and skin contain very little α3(IV) (2,26,27).

The use of purified antigen from tissue or recombinant α3(IV)NC1 domain in diagnostic assays is essential for an accurate diagnosis of anti-GBM disease (1). Crude basement membrane preparations used in many commercial screening assays can result either in misdiagnosis (28) or in a lower sensitivity in patients who do not have robust titers (5). Detailed biochemical and immunologic studies have identified the globular NC1 domain of type IV collagen as the region of α3 chain that binds Goodpasture autoantibodies (1,2,5,26,27,29,30). In a recent study with serum from 58 patients with anti-GBM disease, the primary target for all patients was identified as the α3(IV)NC1 domain (1). Additional antibodies to α1(IV)NC1 and α4(IV)NC1 were present in 15% and 4% of patients, respectively (1). These latter specificities may represent cross-reactive antibodies or antibodies generated in parallel with the α3(IV)NC1 antibodies (1). Most recently, two immunologically privileged peptide regions within the α3(IV)NC1 domain have been identified as epitopes for these autoantibodies (3), and a candidate T-cell epitope has been identified at the N-terminal region of the α3(IV)NC1 domain (8,9).
patients with Goodpasture syndrome demonstrated anti-myeloperoxidase (the major category of p-ANCA) antibodies, whereas only one of 23 (4%) showed a positive serum proteinase (c-ANCA) reactivity. None of the patients with established Wegener’s granulomatosis (28 of them c-ANCA positive, two p-ANCA positive, and one double-positive) tested positive for anti-GBM antibodies. In a larger prospective study, 160 patients with anti-GBM antibody and 1390 patients with ANCA-positivity were serologically evaluated (17) (Table 1). Thirty-four patients had both antibodies, which represented approximately 21% of the anti-GBM population and less than 3% of the ANCA-positive patients. Based on the results of these studies, we estimate that approximately 20% to 30% of patients with anti-GBM disease will test positive for either c-ANCA or p-ANCA, and up to 8% of ANCA-positive patients will have anti-GBM antibodies. Approximately 74% of patients with both ANCA and anti-GBM antibodies are p-ANCA-positive. Our double-positive patient belonged to a smaller group of patients who have c-ANCA and anti-GBM antibodies.

The reason for concurrent ANCA and anti-GBM antibody production in selected patients is not known. It is possible that ANCA-related proteases damage or expose the nephritogenic epitopes in α3(IV) collagen in GBM, and this in turn leads to anti-GBM antibody production. It is unlikely that the cross-reactivity between p-ANCA and anti-GBM antibodies is derived from the same autoantibody repertoire, because there does not appear to be a structural relationship between c-ANCA and α3(IV) NC1 collagen (17). It is currently unclear whether there is any structural cross-reactivity between c-ANCA and anti-GBM antibodies.

Rapid and correct diagnosis of the underlying tissue lesion is essential when both antibody reactivities are present in serum, because, in addition to treatment with high-dose steroids and cyclophosphamide, patients with anti-GBM antibody disease usually require daily plasmapheresis to remove circulating autoantibodies (7). Plasmapheresis should be continued until anti-GBM antibody levels are undetectable, and the usual course is 2 to 4 wk. Immunosuppressive therapy should be administered for approximately 8 wk, and the antibody titers are usually undetectable at this time. If administered early in the disease, this approach has been successful in attenuating progression to end-stage renal failure in as many as 40% of patients (31).

By contrast, plasmapheresis is not considered beneficial in ANCA-positive patients, although anecdotal success has been reported (32). Furthermore, these patients may require a longer course of steroids and cyclophosphamide. This approach is especially applicable to individuals with Wegener’s granulomatosis, other organ system involvement, and a relapsing course. Trimethaprim sulfamethoxazole has been shown to be beneficial in preventing relapses in these patients.

Whether ANCA influences the outcome of patients with anti-GBM disease is uncertain. Bosch et al. (33) reported that patients with anti-GBM disease and anti-myeloperoxidase antibodies (p-ANCA) had a more favorable outcome than patients with anti-GBM antibodies alone, although this finding requires confirmation. In patients with Wegener’s granuloma-
tosis, the presence of anti-proteinase antibodies (c-ANCA, the major category) has been associated with a worse renal outcome (34); however, it is uncertain whether a similar relationship applies to patients with coexistent anti-GBM antibodies.

Acknowledgments

We thank Drs. Betty Phon-Yie Yeh, Gary G. Bluemink at the Chesapeake General Hospital in Chesapeake, and Virginia and J. Charles Jennette at the University of North Carolina for their assistance in providing the case history of the patient and histological slides of the kidney. We also thank Dr. Billy G. Hudson for providing the reference Goodpasture antibodies (LL). This work was supported in part by Grants DK-46282, DK-07006, DK-30280, DK53088, and DK-45191 from the National Institutes of Health, the DCI RED fund, and a National Kidney Foundation fellowship to Dr. Kevin Meyers.

References

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