A Rare Case of Seronegative anti-Glomerular Basement Membrane Disease with Pulmonary Involvement

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ABSTRACT

Seronegative anti-glomerular basement membrane (GBM) disease with pulmonary involvement is exceedingly rare. Most published cases involve patients with extensive smoking histories, and the prognosis is more favorable than classic, seropositive, anti-GBM disease. Herein, we describe the case of a 62-year-old man with a solitary kidney after right nephrectomy who presented with dyspnea, hemoptysis, and severe acute kidney injury. Kidney biopsy was delayed due to negative serologic evaluation, anchoring to a diagnosis of acute tubular necrosis (ATN), and presence of a solitary kidney; however, progressive kidney injury with microhematuria and proteinuria eventually prompted a biopsy that showed crescentic glomerulonephritis with linear GBM staining. The patient started immunosuppressive treatment and responded very well; he remains stable and off dialysis one year after the diagnosis.

KEYWORDS: Seronegative glomerular basement membrane disease; Atypical Goodpasture syndrome; Solitary kidney biopsy; Glomerulonephritis

CASE PRESENTATION

A 62-year-old man with asthma, hypertension, renal clear cell cancer (RCC) status-post right radical nephrectomy, and stage 3b chronic kidney disease with baseline serum creatinine 1.8 mg/dl, presented with dyspnea, hemoptysis, melena, and weakness of several weeks' duration. There was no cigarette smoking history. He was found to have acute kidney injury with serum creatinine 5.1 mg/dl, severe anemia with hemoglobin 3.6 gm/dl, and bilateral ground glass opacities (GGO) with a left lobe subsegmental pulmonary embolism on chest imaging [**Figure 1**]. A urinalysis showed microscopic hematuria with >100 RBCs/hpf and sub-nephrotic proteinuria with urine protein-creatinine ratio 1.2–1.8 g/g. Serologic studies were sent on the day of admission, and these returned negative for glomerular basement membrane (GBM) antibodies, as well as negative ANCA and ANA screens. Bronchoscopy on the second hospital day showed blood on serial lavage, findings consistent with alveolar hemorrhage. Bronchoalveolar lavage fluid cultures were negative. There was no evidence of gastrointestinal bleed on endoscopy. The kidney function transiently stabilized after blood transfusions and a brief course of oral prednisone for presumptive asthma flare. Due to the presence of a solitary kidney, as well as initial anchoring to a diagnosis of acute tubular necrosis (from severe anemia) as a cause of acute kidney injury, a diagnostic kidney biopsy was delayed until two weeks into the admission, at which time the serum creatinine had increased to 6.9 mg/dl. The biopsy showed five glomeruli, of which three contained cellular crescents. There was linear staining of the glomerular capillary walls

Figure 1. [**A**] Axial contrast-enhanced chest CT shows diffuse bilateral ground glass opacities (GGO)at the time of diagnosis. [**B**] Non-contrast CT shows near complete resolution of multifocal airspace disease six months after treatment.

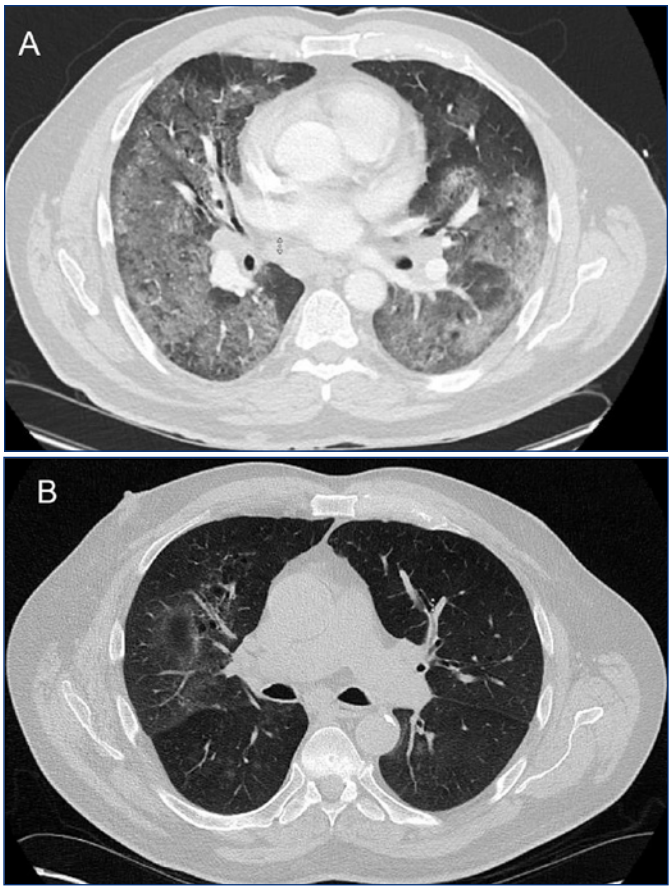
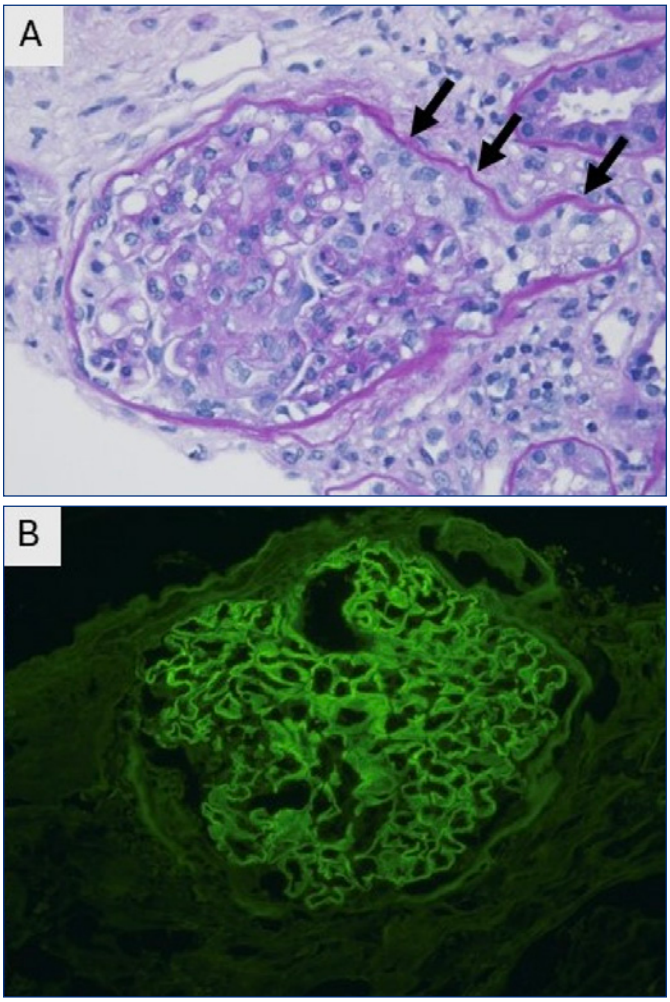


Figure 2. **[A]** Periodic Acid-Schiff (PAS) stain shows a glomerulus with a cellular crescent, marked by black arrows. **[B]** Immunofluorescence stain displays linear staining of glomerular capillary walls for IgG (3+).



with IgG, consistent with crescentic anti-GBM glomerulonephritis [**Figure 2**]. The patient started intravenous methylprednisolone, underwent six sessions of plasmapheresis, and was transitioned to oral cyclophosphamide and prednisone at time of discharge—in accordance with 2021 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines for induction treatment of anti-GBM disease or Goodpasture's syndrome. The serum creatinine improved to 3.7 mg/dl, the hematuria improved, and the proteinuria remained stable at 1.0 g/g. and he did not require dialysis. GBM antibody levels remained negative throughout, and hence they could not be used to track disease activity. Though the post-discharge treatment course was complicated by anemia, requiring several hospitalizations for transfusions, the patient is now off immunosuppression and remains off dialysis one year after the initial diagnosis.

DISCUSSION

Anti-glomerular basement membrane disease is a rare diagnosis with an annual incidence of 1.5 per million people.[1] Patients typically present with a rapidly progressive glomerulonephritis characterized by sub-nephrotic proteinuria, hematuria, and a doubling of serum creatinine over the course of days to weeks, often preceded by a prodromal period of malaise, fatigue, weight loss, and low-grade fevers. The overall patient and renal survival at one year are 80–90% and 26%, respectively, with treatment. In addition to glomerulonephritis, pulmonary hemorrhage is common, occurring in 30–60% of cases.[1] The triad of acute kidney injury, pulmonary hemorrhage, and GBM antibodies is often referred to as Goodpasture's syndrome. The disease is diagnosed by the detection of autoantibodies to components of GBM in the serum, most commonly the non-collagenous domain (NC1) of the alpha-3 subunit of type IV collagen (α3NC1), using conventional enzyme-linked immunosorbent assay (ELISA). On kidney biopsy, there is linear IgG deposition along the glomerular basement membrane on immunofluorescence and a diffuse crescentic glomerulonephritis on light microscopy.[2]

In recent years, several cases of antibody-negative anti-GBM disease have been described, often with atypical clinical presentations such as nephrotic range proteinuria, less severe kidney injury, absent pulmonary involvement, and variable patterns of histological injury on light microscopy.[3–7] Cases where patients who had previous seropositive anti-GBM disease that later became seronegative during disease relapse have also been described.[8] There is speculation as to why anti-GBM antibodies are undetectable in these cases of so-called "atypical anti-GBM disease." One theory is that autoantibodies to different alpha subunits, other than α3NC1, cause disease—there are six subunits in total—and these are undetectable by standard assays. Other theories are that the levels of circulating anti-GBM antibodies are too low or of insufficient affinity to be detected.[6,7] Some groups have successfully run specialized serologic assays for IgG subclasses 1–4 after initially negative or equivocal anti-GBM ELISA to isolate IgG subclasses involved in some atypical cases.[9-11] As was true in our case, patients with atypical anti-GBM disease tend to present with less severe disease and have a more favorable long-term renal prognosis.

Our case presented a unique challenge because the patient had a solitary kidney, which is considered a relative contraindication to kidney biopsy. The risks of native kidney biopsy are well-established. A systematic review and meta-analysis of the literature from 1983 to 2018, including a total of 118,000 kidney biopsies, showed an 11% risk of perinephric hematoma, 3.5% risk of hematuria, 1.6% risk of transfusion, and 0.3% risk of intervention to stop bleeding after biopsy; all these risks were substantially higher in hospitalized patients with acute kidney injury.[12] The study did not specifically examine outcomes in solitary kidney

biopsies or comment on the risk of nephrectomy after biopsy. Only one study reported on the outcomes of eight patients who underwent solitary kidney biopsies—none experienced serious complications.[13] The presence of a solitary kidney is not considered an absolute contraindication to biopsy, and biopsy of a solitary kidney has been utilized in cases of seropositive GBM.[14,15]

The patient presented herein was presumptively diagnosed with ischemic acute tubular necrosis (ATN) based on profound anemia, and his failure to recover kidney function in the first week of admission was attributed to contrast-associated nephropathy. A kidney biopsy was further delayed due to presence of a solitary kidney and the need for anticoagulation for pulmonary embolism, with heparin bridge necessary in advance of the biopsy. Ultimately, a kidney biopsy was essential to make the correct diagnosis and arrive at a treatment plan that has kept the patient free of dialysis for at least one year. The case illustrates the importance of maintaining a high index of suspicion for glomerulonephritis in the appropriate clinical context and never relying solely on serologic studies to rule out glomerular diseases.

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Disclosures

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