Anti-glomerular basement membrane antibody disease treated with rituximab: A case-based review

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Objectives: To report the successful use of rituximab in a patient with anti- glomerular basement membrane (GBM) antibody disease and to review the literature regarding rituximab use in anti-GBM mediated disease.

Methods: We report a case of anti-GBM antibody disease with both anti-GBM antibodies and anti-myeloperoxidase (MPO) specific p-ANCA, who developed thrombotic thrombocytopenic purpura (TTP) on high dose prednisone, plasmapheresis, and cyclophosphamide therapy. The patient was then treated with rituximab. We analyzed the clinical features of five additional patients of anti-GBM disease treated with rituximab identified through a systematic literature review.

Results: Our patient was 68-year-old female who presented with acute renal failure. Renal biopsy showed crescentic glomerulonephritis with linear deposits of IgG antibody along the glomerular basement membrane. Treatment was initiated with high dose prednisone, plasmapheresis and oral cyclophosphamide, with subsequent development of leukopenia and TTP and discontinuance of cyclophosphamide. Treatment with rituximab was initiated with clinical improvement of her hematological parameters but not her renal function. Among the five previously reported cases of anti-GBM disease treated with rituximab, three received brief course of IV cyclophosphamide prior to use of rituximab. Except one patient, all recovered renal function and remained dialysis independent. The anti-GBM antibody level remained undetected in all patients.

Conclusions: Combination of prednisone, plasmapheresis, and rituximab can be an effective therapy in patients with an anti-GBM antibody disease complicated with TTP.

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Anti-GBM antibody disease is a rare auto-immune disorder, estimated to occur in less than one per million people [1–4] and characterized by rapidly progressive glomerulonephritis. The term Goodpasture's disease is often reserved for those patients with glomerulonephritis, pulmonary hemorrhage, and anti-GBM antibodies [5]. The name Goodpasture's disease was first used by Stanson and Tange in 1950, who described patients with renal and pulmonary features as first reported by Ernest Goodpasture, an American pathologist [5]. The pathognomonic finding is a linear IgG deposits along the basement membrane resulting from anti-GBM antibodies which are specific to the non-collagen domain 1 (NC1) of the α3 region of the type 4 collagen [6]. These antibodies have been shown to be pathogenic in passive transfer experiments in which antibodies obtained from the plasma of patients produced glomerulonephritis when infused into animals [7].

There is a bimodal age distribution with the first peak approximately at 30 years of age and a 2nd peak at 60 years [2]. Patients in their 60s and 70s account for greater than 20% of all patients of all anti-GBM antibody disease. Compared to younger patients, the prevalence of pulmonary hemorrhage is lower in this older group. Renal outcomes are, however, similar to those in the younger group and the survival is worst [8].

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In the absence of treatment, patients with anti-GBM renal disease rapidly progress to end stage renal disease or death. The ability of these antibodies to bind rapidly and tightly to the glomerular basement membrane (GBM) may underlie the typically fulminant nature of this disease. Conventional treatment with plasma exchange in combination with prednisone and cyclophosphamide has improved the outcome significantly [9,10]. However, this combination therapy is associated with significant side effects including marrow suppression, risk of infection and hemorrhagic cystitis. Rituximab has been reported to be used in an antibody mediated autoimmune diseases including anti-GBM antibody disease [11–13]. Decreased incidence of toxicity and enhanced clinical effectiveness suggests that a B cell depleting agent may have an advantage over traditional immunosuppressive agents.

We describe a patient with anti-GBM antibody disease treated with rituximab along with steroid and plasmapheresis therapy to suppress antibody production.

METHODS

We conducted a search on the PubMed database using combination of the following terms. Good Pasture's, Rituximab, anti-GBM antibody disease, thrombotic thrombocytopenic purpura and ANCA-associated vasculitis. We evaluated all series, reviews and case reports in which diagnosis of anti-GBM antibody disease was related to treatment with rituximab. We found three articles (published from 2002 to Jan 2011) that reported patients who developed anti-GBM disease and received treatment with rituximab.

Case presentation

A 68-year-old female presented to the emergency department with a 3-week history of progressive weakness and anuria. She was otherwise healthy until 3 weeks prior to evaluation when she started having malaise, loss of appetite, nausea, joint pain and low grade fever that she attributed to a flu-like illness. Her symptoms of nausea and vomiting worsened during the week prior to her admission, causing her to be evaluated in the emergency room. Her past medical history was remarkable for mild coronary artery disease. She reported taking aspirin and metoprolol at the time of admission, albeit, not always on a regular basis.

At the time of admission her heart rate was 82 beats/min and regular, her respiratory rate was18 min, and her blood pressure was 135/80. Lungs were clear to auscultation. Cardiac rhythm and heart sounds were normal without murmur or gallop. Neurological exam was normal. Skin exam did not reveal any rash. Musculoskeletal exam revealed no joint swelling or tenderness and she had no peripheral edema.

The patient's admission blood tests are summarized in Table 1. Urinalysis was not available due to anuria. The patient was found to have acute renal insufficiency with a serum creatinine of 11.3 mg/dL. The C-reactive protein (CRP) was 17.4 mg/dL and erythrocyte sedimentation rate (ESR) was 45 mm/h. Assays for ANA, HIV, Hepatitis C virus antibody, and Hepatitis B surface antigen were negative. Computed tomography (CT) of the chest without contrast showed normal lung parenchyma with bilateral pleural effusion. CT of the abdomen without contrast revealed no hydronephrosis.

Clinical course

The patient was initially treated with intravenous fluid (IVF) without improvement in urine output. Her creatinine decreased to 7.3 mg/dL following hydration with IVF. Renal replacement therapy with hemodialysis was instituted on day 3 of her hospitalization. A working diagnosis of acute renal insufficiency secondary to acute glomerulonephritis was considered and empiric therapy with intravenous methylprednisolone was initiated on day 3 of her hospitalization (1000 mg/day for 3 days) followed by oral prednisone at 1 mg/kg/day. Anti-GBM antibodies were detected at a titer of 1:160. ANCA was

Table 1

Lab Test	Patient Lab Value	Normal
Hemoglobin (g/dL)	12	12–15
WBC count (cells/L)	8.7	$4.5–11.5 \times 10^9$
Platelets (cells/L)	553	$150–400 \times 10^9$
Albumin (g/dL)	2.4	3.5–4.8
Protein, total (g/dL)	5.7	5.7–8.1
Anti-GBM titer	>1:160	(<1:20)
P-ANCA	>1:160	(<1:20)
MPO (P-ANCA)	48	>30 U Positive
Creatinine (mg/dL)	11.30	0.70–1.50
Sodium (mmol/L)	117	135–148
ADAMTS13 activity	<5%	>66%
Haptoglobin (mg/dL)	<15	36–220
LDH IU/L	243	50–220
Direct Coomb's test	Negative	Negative