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Exceptional Case

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Rituximab for the treatment of refractory simultaneous anti-glomerular basement membrane (anti-GBM) and membranous nephropathy

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Abstract
Antibody-mediated anti-glomerular basement membrane (anti-GBM) disease occurs rarely in the presence of another B-cell disorder, membranous nephropathy. The coexistence of these two autoimmune disorders would be anticipated to require differing, specific therapies targeted to each disease process. We describe a case of concomitant membranous nephropathy and anti-GBM disease in which conventional therapy, including steroids, plasmapheresis and cyclophosphamide, failed to attenuate the anti-GBM disease, yet responded to an alternative treatment of rituximab. This B-cell directed, monoclonal, chimeric antibody treatment substantially reduced anti-GBM antibody titers and led to discontinuation of plasmapheresis, while maintaining the remission of membranous nephropathy and anti-GBM disease.

Keywords: anti CD-20; anti-GBM disease; Goodpasture syndrome; membranous nephropathy, rituximab

Introduction

Goodpasture syndrome (GPS) was first identified in 1959 by Drs Stanton and Tange, with the description of nine patients with renal failure and pulmonary hemorrhage, all of whom eventually died [1]. Subsequently, the molecular basis of this disease was found to be auto-antibodies formed against the α3 and α5 domains within the non-collagenous part of type IV collagen present in basement membranes of glomeruli and alveoli. The incidence of GPS is roughly 0.5–1 per million in patients of Caucasian race [2]. It represents 1–5% of all glomerulonephritis cases and 10–20% of crescentic glomerulonephritis cases [3]. Left untreated, GPS carries a poor prognosis [2]. Conventional treatment for anti-glomerular basement membrane (GBM) disease includes both immunosuppression and plasma exchange. However, because of the infrequent nature of anti-GBM disease, there is a paucity of randomized clinical trial data with which to inform and optimize therapy. Nonetheless, a small, randomized trial in 1985 of 17 subjects revealed the superiority of immunosuppressive therapy in combination with plasma exchange versus immunosuppression alone. It is this trial that forms the basis of current treatment recommendations for this disease [4].

Rituximab is a chimeric monoclonal antibody directed against CD-20 positive B-cells. Following infusion, rapid B-cell lysis occurs with consequent decline in antibody production, antigen presentation and activation of T-cells and macrophages [5]. We present a case of concurrent anti-GBM disease and membranous nephropathy, which was resistant to conventional therapy, yet treated successfully with rituximab.

Case report

A 24-year-old Caucasian male, without a significant past medical history, presented with a 2-week history of hematuria and occasional expectoration of blood-tinged sputum. He reported a smoking history of ~1 pack per day for the past 5 years. Physical examination revealed the following vital signs: temperature of 36.5°C, heart rate of 78 bpm, blood pressure of 131/82 mmHg and respiratory rate of 18 per minute with 99% saturation on room air. He had clear lung fields, no peripheral edema and had no rash.

Laboratory evaluation showed the following values: hemoglobin 1.7 mmol/L (11.0 g/dL), hematocrit 32.4%, WBC 10.5 K/μL, platelets 227 K/μL, sodium 138 mmol/L, potassium 4.3 mmol/L, chloride 100 mmol/L, serum creatinine (SCr) 247.35 μmol/L (2.8 mg/dL) and a glucose level of 5.49 mmol/L (99 mg/dL). The SCr rose to 379.86 μmol/L (4.3 mg/dL) over 4 days despite volume expansion with intravenous fluids. A chest radiograph, obtained on admission, was interpreted as within normal limits. The examination of the urine sediment disclosed red blood cell casts. His initial urine albumin-to-creatinine ratio (ACR) was 1004 mg/g. He had normal complement levels with

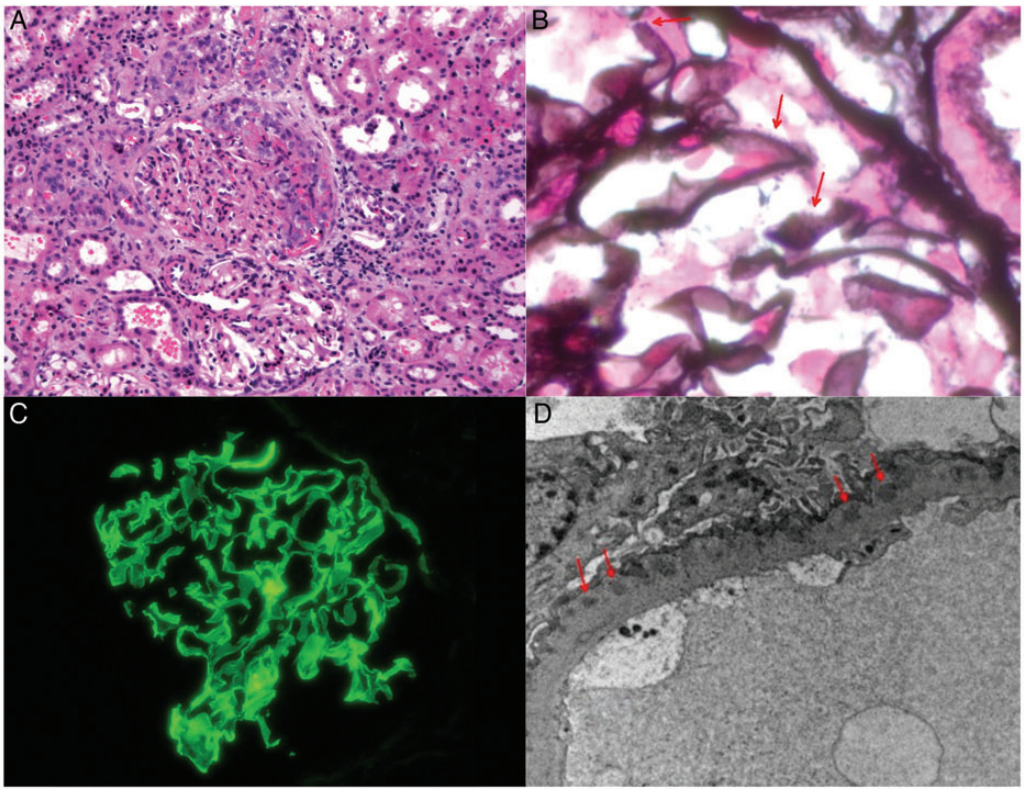

Fig. 1. Hematoxylin and eosin staining of renal biopsy specimen from a patient with concurrent diagnoses of anti-GBM disease and idiopathic membranous nephropathy that demonstrates a glomerular crescent; original magnification ×200 (**A**). Jones methenamine silver stain of the same biopsy specimen with epimembranous 'spikes' delineated by arrows, original magnification ×600 (**B**). Linear immunofluorescent staining of GBM by anti-human rabbit immunoglobulin G; original magnification ×400 (**C**). Electron-dense epimembranous deposits shown by arrows; original magnification ×15 750 (**D**).

C3 and C4 levels of 160 mg/dL (normal range, 90–230) and 29 mg/dL (normal range, 10–51), respectively. His erythrocyte sedimentation rate was elevated at 53 mm/h. Other negative tests included the following: antinuclear antibody, anti-neutrophilic cytoplasmic antibody, anti-DNA antibody, rheumatoid factor, human immunodeficiency virus antibody, hepatitis C antibody and hepatitis B surface antigen. Anti-GBM titers were pending at the time of kidney biopsy.

The kidney biopsy (Figure 1) revealed a crescentic glomerulonephritis with 54% of 13 glomeruli demonstrating cellular crescents and linear IgG staining of the glomerular capillary basement membrane characteristic of anti-GBM disease, along with faint capillary loop granular staining. Electron microscopy confirmed the presence of occasional small epimembranous and intramembranous electron dense deposits characteristic of membranous nephropathy.

Daily apheresis treatments were initiated and were reduced to a thrice-weekly regimen after three consecutive treatments. Initial anti-GBM titer was 161 units (normal < 21). He was transitioned to prednisone 60 mg daily by mouth, after 3 intravenous pulse doses of 1 g methylprednisolone and oral, daily cyclophosphamide (CYC) 250 mg (2.5 mg/kg) that was soon reduced to 150 mg daily after adjustment for renal function. Approximately 2 weeks after admission, he was discharged on prednisone 60 mg daily, CYC 150 mg daily and thrice-weekly apheresis treatments. At discharge, the SCr was 459.36 µmol/L (5.2 mg/dL) and the anti-GBM titer was 86 units.

Following two apheresis treatments, the patient's kidney function deteriorated. His SCr increased to 644.88 µmol/L (7.3 mg/dL) and his anti-GBM titer rose to 132 units. The patient also became volume overloaded. This led to readmission for initiation of hemodialysis, along with daily apheresis. He received 17 apheresis treatments during his second hospitalization, on a near daily basis. He also received four hemodialysis treatments that were eventually stopped due to substantial improvement in his kidney function. His SCr stabilized around 397.53 µmol/L (4.5 mg/dL) with a creatinine clearance of 26 mL/min/1.73 m^2 determined by a 24-h urine collection. He was discharged again on a thrice-weekly apheresis schedule. He was maintained on CYC 150 mg daily and prednisone 60 mg daily. His last anti-GBM titer before discharge was 59 units. Although the SCr declined to 362.19 µmol/L (4.1 mg/dL), the anti-GBM titer was persistently elevated. The

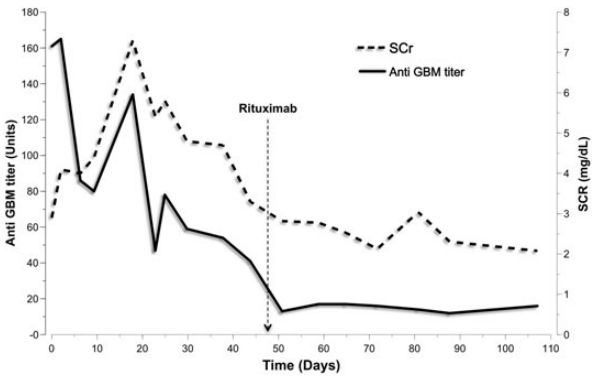

Fig. 2. Relationship among anti-GBM titers, SCr and time.

patient remained apheresis-dependent and attributable to the lack of response to conventional therapy, B-cell depletion with rituximab was attempted to eliminate antibody production. Approximately 2 months after his initial presentation, the patient received a single, 1000 mg dose of rituximab. Subsequently, the patient's anti-GBM titer normalized (Figure 2), and the patient was maintained on CYC and prednisone. The apheresis treatment frequency was slowly decreased and then stopped. The last treatment was administered 3 months after his initial presentation. CYC was stopped after 6 months at 21.7 g for a total cumulative dose. Prednisone was slowly reduced and ultimately discontinued over a 6-month time period. Presently, his SCr is 181.98 µmol/L (2.06 mg/dL) and the ACR is 366 mg/g on maximal dose lisinopril therapy. The patient's course is summarized in Figure 3.

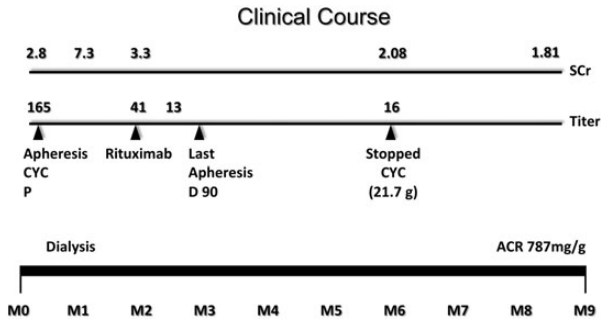

Fig. 3. ACR, albumin-to-creatinine ratio; CYC, cyclophosphamide; D, day; M, month; P, prednisone; SCr, serum creatinine (mg/dL); Titer reported in units.

Discussion

Our patient experienced a rapidly progressive course typical of anti-GBM disease eventuating in hemodialysis. He also manifested membranous nephropathy. The treating care providers opted initially for a treatment regimen consisting of apheresis, CYC and prednisone. The CYC plus prednisone approach has been one of the main regimens to treat membranous nephropathy [6], and initially, we felt that this approach would provide efficacious treatment of both glomerulopathies. Simultaneous anti-GBM disease and membranous nephropathy has been reported infrequently. A review published in 2011 reported a case of concurrent anti-GBM disease and membranous nephropathy and reviewed 25 previously reported cases [7]. More recently, the etiopathogenesis of idiopathic membranous nephropathy has been characterized and determined to result from auto-antibodies directed against the podocyte-related antigen, phospholipase A2 [8–10]. Previously, Basford *et al*. [7] hypothesized that concurrent disease resulted from the induction of one disorder from the other. It is also possible that a biclonal autoimmune response is responsible for the simultaneous occurrence of anti-GBM disease and membranous nephropathy. Biclonality is a rare but established phenomenon and has been described in multiple myeloma and lymphomas [11].

The index patient demonstrated a clear correlation between his anti-GBM titers and his kidney function

Table 1. Summary of anti-GBM cases reporting the use of rituximab

	Case	Lung involvement	Anti-GBM titer before treatment	Treatment	Anti-GBM titer after treatment	Outcome
Weschler *et al.*	55-year-old male with HIV	No symptomatic lung involvement	8.6 EU/dL (NL < 5)	P, MMF, IVIG, 375 mg/m^2 Rituximab 4 weekly doses	Negative for 16 months of follow-up	SCr 1.2 mg/dL at 16 months follow-up
Arzoo *et al.*	73-year-old female with GPS relapse after 1-year remission	Clinical lung involvement	51 IU/dL	PLEX, P and CYC, followed by rituximab 375 mg/m^2, 6 weekly doses, followed by azathioprine maintenance after 4th cycle	Negative	In remission after 10 months
Shah *et al.*	54-year-old male, anti-GBM disease dialysis-dependent at outset	Overt lung hemorrhage	>680 U/mL	PMP, PLEX, CYC that was switched to rituximab 375 mg/m^2 4 weekly doses	Negative	Dialysis-dependent and on transplant list
Shah *et al.*	64-year-old male, anti-GBM disease, p-ANCA positive, required dialysis, initial SCr 6.37 mg/dL (536 µmol/L)		49 U/mL	High-dose steroids, PLEX, CYC converted to rituximab 375 mg/m^2, 4 weekly doses	Negative	Dialysis-independent with SCr 2.94 mg/dL (260 µmol/L)
Shah *et al.*	17-year-old male anti-GBM disease, initial SCr 3.08 (272 µmol/L)	Clinical lung involvement	131 U/L (NL < 3)	Four doses of PMP, PLEX, and 2 weekly doses of rituximab 375 mg/m^2	Negative	SCR 1.13 mg/dL after 33 months
Syeda *et al.*	68-year-old female dialysis-dependent, SCr 11.3 mg/dL, p-ANCA positive developed TTP	No lung involvement	Anti-GBM Ab >1:160, NL < 1:20	PLEX, P, CYC (5 days), 4 doses of rituximab 375 mg/m^2	Negative	Dialysis-dependent
Sauter M. *et al.*	29-year-old, male status post-DDKT because of Goodpasture's, presented with AKI 16 mo post-transplant	No symptomatic lung disease after recurrence	95.5 IU/dL (NL < 4)	PLEX, MMF dose escalation to 3 g/d, and P After 2 weeks MMF substituted by CYC rituximab 375 mg/ for 3 weekly doses		Loss of renal graft, patient on RRT

Ab, antibody; ACR, albumin-to-creatinine ratio; ANCA, antineutrophil cytoplasmic antibody; CYC, cyclophosphamide; DDKT, deceased donor kidney transplant; GBM, glomerular basement membrane; GPS, Goodpasture syndrome; HIV, human immunodeficiency virus; IVIG, intravenous immunoglobulin; mo, month(s); MMF, mycophenolate mofetil; NL, normal; P, prednisone; PLEX, plasma exchange; RRT, renal replacement therapy; SCr, creatinine (mg/dL); TTP, thrombotic thrombocytopenic purpura; wk, week(s); U, antibody titer units.

(Figure 2). Our patient's initial presenting anti-GBM titers were highly elevated (nine times the reference range) but minimally responsive to conventional therapy (CYC and prednisone). Since he was apheresis-dependent and required renal replacement therapy, conventional therapy was considered a failure. Given the persistence of the anti-GBM titer, the alternative anti-CD20 B-cell depletion treatment represented a plausible and rational option in this disorder. There has been increasing evidence that rituximab is effective for the treatment of membranous nephropathy [12–14], and this treatment has been efficacious in six of seven isolated cases of anti-GBM disease (Table 1) [15–19]. This report represents the seventh successful instance of rituximab treatment of anti-GBM disease and the second case where independence from renal replacement therapy was achieved. Moreover, this is the first case where rituximab has been used as simultaneous treatment of coexistent membranous nephropathy and anti-GBM disease.

The index patient, formerly dialysis- and apheresis-dependent, is now apheresis-independent and completed CYC and prednisone therapies after just a single rituximab treatment. The proteinuria nearly completely resolved and the SCr stabilized at 181.98 μmol/L (2.06 mg/dL). We contend that rituximab has induced a coincident and complete remission of his two separate glomerulopathies. Lastly, given the positive outcomes of this case and the pathobiology of anti-GBM disease, we suggest B-Cell depletion therapy as an alternative treatment modality in refractory anti-GBM disease.

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Conflict of interest statement. None declared.

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