Clinical Kidney Journal, 2015, vol. 8, no. 4, 445–448

doi: 10.1093/ckj/sfv044
Advance Access Publication Date: 15 June 2015
Exceptional case

EXCEPTIONAL CASE

Eculizumab-induced reversal of dialysis-dependent kidney failure from C3 glomerulonephritis

Melissa Inman[1], Ginnie Prater[1], Huma Fatima[2], and Eric Wallace[1]

[1]Department of Medicine, Division of Nephrology, University of Alabama at Birmingham, Birmingham, AL, USA, and [2]Department of Pathology, University of Alabama at Birmingham, Birmingham, AL, USA

Correspondence to: Eric Wallace; E-mail: mainman@uabmc.edu

Abstract

C3 glomerulopathy (C3G) is characterized by C3 deposits with minimal immunoglobulin deposition caused by alternative complement pathway dysregulation. Unfortunately, no therapeutic intervention has consistently improved outcomes for patients with C3G. Eculizumab, a monoclonal antibody to C5, is currently the only approved complement-specific agent with some efficacy in the treatment of C3 glomerulonephritis (C3GN). Here, we describe a patient with acute crescentic C3GN with no identified complement mutation or family history of renal disease who required dialysis for 6 months. Five months after initiation of eculizumab, she became dialysis independent, showing improvement is possible after adequate time on eculizumab.

Key words: alternative pathway, C3 glomerulopathy, complement, eculizumab, end-stage renal disease

Introduction

Dysregulation of the alternative pathway (AP) of complement causes a spectrum of kidney diseases ranging from atypical hemolytic uremic syndrome (aHUS) to C3 glomerulopathy (C3G) [1–3]. C3G encompasses all glomerular lesions characterized by predominant C3 deposits with little to no immunoglobulin deposition and include C3 glomerulonephritis (C3GN) and dense deposit disease (DDD) [4]. Both C3GN and DDD carry a poor prognosis with rates of progression to end-stage renal disease (ESRD) reported in up to 50% of patients with C3GN [5] and DDD [6, 7]. Furthermore, recurrence rates in transplant can be as high as 66.7% of patients with C3GN [8] and up to 70% of patients with DDD [7]. Due to these allograft recurrence rates, therapies are needed to slow or prevent progression to ESRD [5, 9, 10]. Unfortunately, therapeutic options are limited. Small trials with anticellular immune therapies with or without plasma therapy have shown little efficacy at preventing progression as well as recurrence of C3G [6, 10, 11]. Eculizumab, a humanized monoclonal antibody to C5, has been used successfully in the treatment of other complement-mediated diseases such as aHUS and paroxysmal nocturnal hemoglobinuria [12, 13]. There are limited data showing some efficacy in the treatment of patients with DDD and C3GN [14]. Here, we report a case of C3GN who after 5 months of eculizumab therapy and dialysis was rendered dialysis independent and remains as such 1 year later.

Clinical history

A 38-year-old woman with a history of recurrent idiopathic urticaria and well-controlled Type II diabetes mellitus was sent to the emergency room by her primary care physician for a blood pressure of 215/110 mmHg. The patient was noted to have periorbital and lower extremity edema with the remainder of her physical exam unremarkable. Laboratory evaluation revealed a serum creatinine of 11.0 mg/dL (972.4 mmol/L) [estimated glomerular filtration rate was 5 mL/min/1.73 m^2 by the 4-variable Modification

Received: March 23, 2015. **Revised:** May 20, 2015. **Accepted:** May 26, 2015

of Diet in Renal Disease (MDRD) Study equation], up from a creatinine of 0.5 mg/dL (88.4 mmol/L) 10 months prior to presentation, and blood urea nitrogen of 66 mg/dL (24 mmol/L). Urinalysis dipstick showed 4+ protein and 3+ blood with 20–50 red blood cells per high-power field. A spot urinary protein-to-creatinine ratio was 6.82 g/g. Hemoglobin was 6.6 g/dL (4.1 mmol/L); platelet count 223 K/mm^3 and serum albumin 2.8 g/dL (28 g/L). Levels of complement proteins C3 and C4 were normal. Evaluation for hepatitis B surface antigen, hepatitis B core antibody, hepatitis C antibody, antinuclear antibody, antineutrophil cytoplasmic antibody and serum cryoglobulins were negative. Urine protein electrophoresis and immunofixation electrophoresis showed a free lambda light chain. Serum free lambda light chain was markedly elevated at 901 mg/L with a very low ratio at 0.09. Renal ultrasound revealed bilateral 13 cm × 6 cm kidneys. The patient was started on hemodialysis 4 days after presentation due to worsening renal failure. Empiric treatment with 500 mg of intravenous methylprednisolone daily for 5 days was followed by prednisone 60 mg daily in divided doses.

Kidney biopsy

A kidney biopsy revealed 49 glomeruli, one globally sclerosed, with moderate to marked nodular mesangial expansion with increased silver negative matrix and mild hypercellularity. Twenty-three glomeruli had cellular crescents but no fibrinoid necrosis or endocapillary hypercellularity and of these, 14 had segmental sclerotic lesions. There was mild interstitial fibrosis and mild-to-moderate vascular changes. (Figure 1A) A Congo red stain was negative. Immunofluorescence revealed strong mesangial staining for C3 diffusely without evidence of immunoglobulins, light chains or C1q (Figure 1B). Electron microscopy revealed numerous large ill-defined mesangial and occasional small subendothelial electron-dense deposits and diffuse effacement of podocytes (Figure 1C). The final diagnosis was C3 glomerulonephritis.

Clinical follow-up

The patient failed to improve clinically after three weeks and was transferred to the university hospital. Functional and genetic studies of the AP of complement were performed at the University of Iowa as previously described [15] and revealed an elevated soluble membrane attack complex (sMAC) level of 0.36 mg/L (reference range, <0.3 mg/L) as well as a positive complement hemolytic assay 6.17% (reference range, <3%), indicating abnormal surface regulation of the AP in our patient. Additionally, the patient was found to be homozygous for the *CFHR3-CFHR1 deletion polymorphism*. Evaluation for an FH autoantibody or C3 nephritic factor was negative. Free lambda value improved to 45 mg/L and light chain ratio normalized. The patient also tested negative for gene mutations encoding for complement factors H, I and B as well as C3, membrane cofactor protein, complement factor H-related protein 5, thrombomodulin, diacylglycerol kinase-epsilon, plasminogen and ADAMTS13.

Due to her acute presentation, minimal fibrosis on biopsy, and likelihood of recurrence in a future allograft, aggressive management was instituted. Plasmapheresis was initiated for three treatments given some success previously reported in patients with C3G [16, 17]. After the third plasmapheresis, eculizumab was initiated at 900 mg weekly for 4 weeks then 1200 mg every other week. The patient received the meningococcal vaccine prior to starting eculizumab followed by prophylactic ciprofloxacin for 14 days. The patient remained dialysis dependent during her hospitalization and was transitioned to peritoneal dialysis prior to discharge.

After initiation of eculizumab, renal function and proteinuria improved (Figure 2). Five months after initiation of therapy, dialysis was discontinued and 24-h creatinine clearance was 34 mL/min with 2.04 gm/day of proteinuria. The patient's renal function continued to improve off dialysis with a serum creatinine of 2.3 mg/dL and an estimated glomerular filtration rate of 29 mL/min/1.73 m^2.

Discussion

The diagnosis of C3G is dependent upon C3 dominant staining with minimal immunoglobulin staining on kidney biopsy. This pattern implicates uncontrolled activation of the AP of complement in the pathogenesis of these diseases [3]. To maintain complement homeostasis and prevent nonspecific cell damage when the AP is activated, typically there is accelerated dissociation of the AP C3 convertase and inactivation of C3b by proteins present in plasma and on cell membranes, limiting the location and activity of complement.

Many patients with C3G have identified acquired or genetic defects associated with AP dysregulation [18]. These defects include mutations in complement genes (encoding for factor H, factor I, factor B and C3) or acquired autoantibodies that either stabilize C3 convertase (C3 nephritic factors) or affect the inhibitory complement factors (factor H autoantibodies), leading to dysregulation of the AP C3 convertase, with variable concomitant dysregulation of C5 convertase [3, 19]. Due to the heterogeneity in pathogenesis, evaluation of serum C3 and C4 levels, factor H and C3 nephritic factor are recommended [20]. Another possibility of complement activation exists in this patient in that lambda light chains have been shown to prevent CFH binding to C3b, thereby leading to AP dysregulation [21].

The therapeutic options for patients with C3G are limited and previous studies are difficult to interpret due to the heterogeneous patient population. Basic measures have included renin–angiotensin blockade to reduce proteinuria [6]. Immunosuppressive therapy has had little success in changing renal outcomes, while plasmapheresis has had limited success in patients with identified autoantibodies or with complement factor H mutations [6, 11, 14, 16, 17, 22].

Eculizumab is a humanized monoclonal antibody that binds to C5 and prevents the generation of membrane attack complex (MAC), the common terminal pathway of complement-mediated injury in all types of C3G. Few case reports and one open-label studies have reported successful treatment with eculizumab in patients with C3GN and DDD [14, 22, 23], indicating eculizumab treatment may be appropriate for some patients with C3G. Based on these limited studies, measurement of sMAC may help predict patient response to eculizumab [14, 24, 25]. Other clinical factors that may predict response to eculizumab include short disease duration and active inflammatory lesions with limited fibrosis on kidney biopsy [14, 20]. All of these features were present in the case described.

The response time to eculizumab therapy remains largely unknown for patients with C3G. However, parallels might be drawn from treatment of aHUS given the common pathogenesis of AP dysregulation. In two prospective trials studying the use of eculizumab in aHUS, treatment duration included an initial 26-week trial of eculizumab with additional long-term extension phases lasting 62–64 weeks [12]. Significant improvements in renal function and proteinuria were seen throughout the initial 26-week period, and many continued to improve through the 64 week

Clinical Kidney Journal

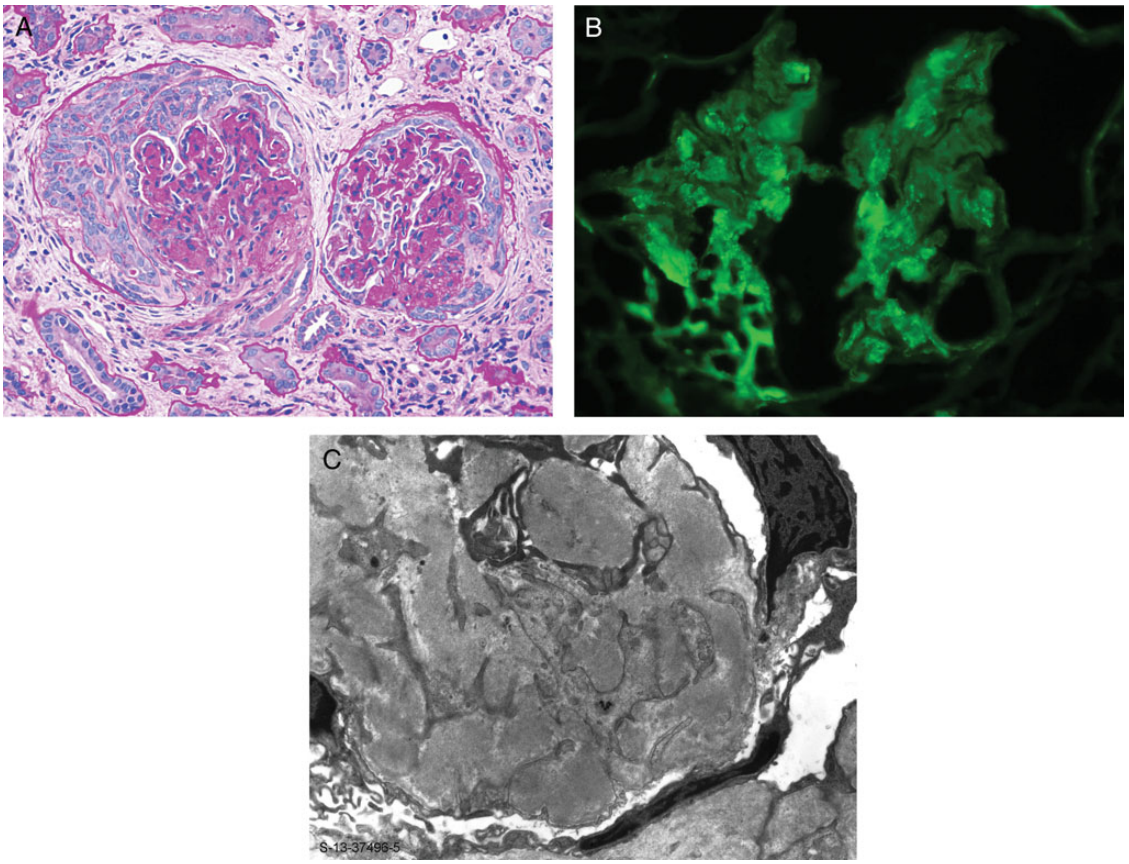

Fig. 1. (**A**) Two glomeruli showing early fibrocellular crescents; well formed (left) and incipient (right). There is moderate increase in mesangial matrix but mesangial cellularity is only mildly increased. The glomerular basement membranes are thickened due to double contour and cellular interposition, without any breaks. The glomerulus on the right is also showing a segmental sclerotic lesion and periglomerular fibrosis. The surrounding interstitium is showing fibrosis and mild inflammatory infiltrate with associated early tubular atrophy and rare tubulitis (Periodic acid Schiff-hematoxylin stain, ×200). (**B**) There is strong chunky and granular predominantly mesangial and rare granular capillary loop staining for C3 (anti-C3 immunofluorescence, ×400). (**C**) The expanded mesangium is showing numerous large ill-defined electron-dense deposits without increased mesangial cellularity. The foot processes are completely effaced (transmission electron microscopy, ×7000).

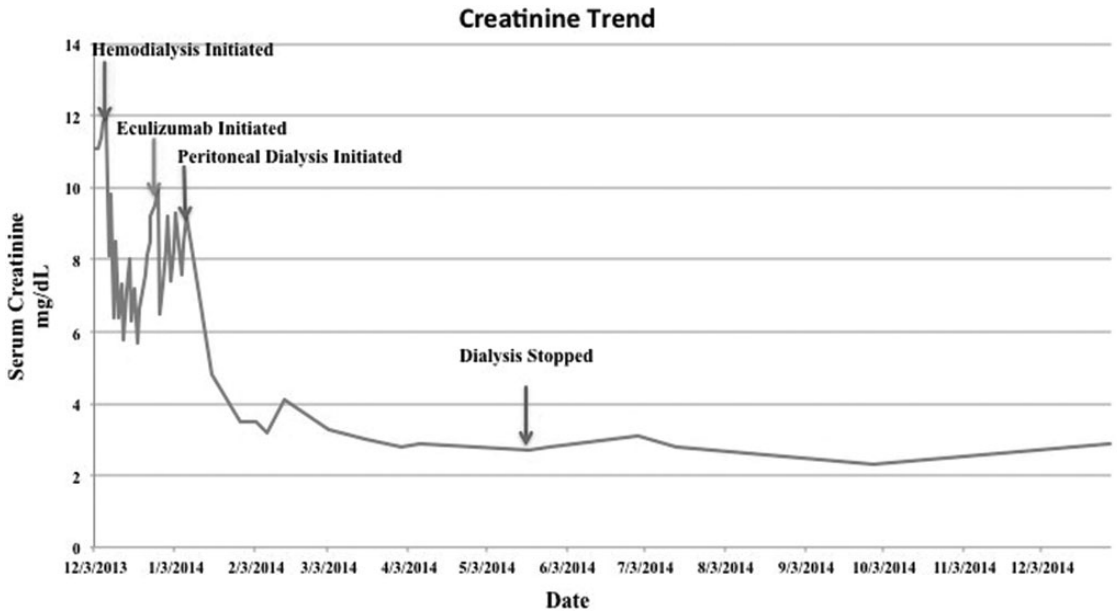

Fig. 2. Trend of patient's creatinine throughout the duration of her illness showing long-term response to eculizumab therapy.

cut-off date [12]. Limited data in C3G support prolonged therapy with eculizumab may be necessary prior to seeing results [14]. Our patient required eculizumab therapy for 5 months prior to developing renal recovery. Data from these studies as well as our case report suggest a long therapeutic trial of at least 6 months on eculizumab is needed to assess response to therapy. However, reporting bias may be present in the literature, and in order to evaluate if this response is applicable to all patients with C3G, controlled studies are needed.

In conclusion, eculizumab may be appropriate in patients with C3GN with limited duration and minimal fibrosis on kidney biopsy. A minimum of 6 months of therapy may be necessary prior to declaring treatment failure.

Conflict of interest statement

None declared.

(See related article by Rodriguez-Osorio and Ortiz. Timing of eculizumab therapy for C3 glomerulonephritis. *Clin Kidney J* (2015) 8: 449–452.)

References

1. Sethi S, Fervenza FC, Zhang Y *et al*. Proliferative glomerulonephritis secondary to dysfunction of the alternative pathway of complement. *Clin J Am Soc Nephrol*2011; 6: 1009–1017
2. Pickering M, Cook HT. Complement and glomerular disease: new insights. *Curr Opin Nephrol Hypertens* 2011; 20: 271–277
3. Sethi S, Fervenza FC. Pathology of renal diseases associated with dysfunction of the alternative pathway of complement: C3 glomerulopathy and atypical hemolytic uremic syndrome (aHUS). *Semin Thromb Hemost* 2014; 40: 416–421
4. Fakhouri F, Frémeaux-Bacchi V, Noël L-H *et al*. C3 glomerulopathy: a new classification. *Nat Rev Nephrol* 2010; 6: 494–499
5. Servais A, Noël L-H, Frémeaux-Bacchi V *et al*. C3 glomerulopathy. *Contrib Nephrol* 2013; 181: 185–193
6. Smith RJH, Alexander J, Barlow PN *et al*. New approaches to the treatment of dense deposit disease. *J Am Soc Nephrol* 2007; 18: 2447–2456
7. Lu D-F, Moon M, Lanning LD *et al*. Clinical features and outcomes of 98 children and adults with dense deposit disease. *Pediatr Nephrol* 2012; 27: 773–781
8. Zand L, Lorenz EC, Cosio FG *et al*. Clinical findings, pathology, and outcomes of C3GN after kidney transplantation. *J Am Soc Nephrol*2014; 25: 1110–1117
9. Medjeral-Thomas NR, O'Shaughnessy MM, O'Regan JA *et al*. C3 glomerulopathy: clinicopathologic features and predictors of outcome. *Clin J Am Soc Nephrol*2014; 9: 46–53
10. Nasr SH, Valeri AM, Appel GB *et al*. Dense deposit disease: clinicopathologic study of 32 pediatric and adult patients. *Clin J Am Soc Nephrol* 2009; 4: 22–32
11. Nester CM, Smith RJ. Treatment options for C3 glomerulopathy. *Curr Opin Nephrol Hypertens* 2013; 22: 231–237
12. Legendre CM, Licht C, Loirat C. Eculizumab in atypical hemolytic-uremic syndrome. *N Engl J Med* 2013; 369: 1379–1380
13. Hillmen P, Young NS, Schubert J *et al*. The complement inhibitor eculizumab in paroxysmal nocturnal hemoglobinuria. *N Engl J Med* 2006; 355: 1233–1243
14. Bomback AS, Smith RJ, Barile GR *et al*. Eculizumab for dense deposit disease and C3 glomerulonephritis. *Clin J Am Soc Nephrol* 2012; 7: 748–756
15. Abrera-Abeleda MA, Nishimura C, Frees K *et al*. Allelic variants of complement genes associated with dense deposit disease. *J Am Soc Nephrol* 2011; 22: 1551–1559
16. Kurtz KA, Schlueter AJ. Management of membranoproliferative glomerulonephritis type II with plasmapheresis. *J Clin Apheresis* 2002; 17: 135–137
17. Habbig S, Mihatsch MJ, Heinen S *et al*. C3 deposition glomerulopathy due to a functional factor H defect. *Kidney Int* 2009; 75: 1230–1234
18. Barbour TD, Pickering MC, Cook HT. Recent insights into C3 glomerulopathy. *Nephrol Dial Transplant*2013; 28: 1685–1693
19. Appel GB, Appel AS. New diagnostic tests and new therapies for glomerular diseases. *Blood Purif* 2013; 35: 81–85
20. Pickering MC, D'Agati VD, Nester CM *et al*. C3 glomerulopathy: consensus report. *Kidney Int* 2013; 84: 1079–1089
21. Sakari Jokiranta T, Solomon A, Pangburn M *et al*. Nephritogenic lambda light chain dimer: a unique human miniautoantibody against complement factor H. *J Immunol* 1999; 163: 4590–4596
22. Radhakrishnan S, Lunn A, Kirschfink M *et al*. Eculizumab and refractory membranoproliferative glomerulonephritis. *N Engl J Med* 2012; 366: 1165–1166
23. Vivarelli M, Pasini A, Emma F. Eculizumab for the treatment of dense-deposit disease. *N Engl J Med* 2012; 366: 1163–1165
24. Gurkan S, Fyfe B, Weiss L *et al*. Eculizumab and recurrent C3 glomerulonephritis. *Pediatr Nephrol Berl Ger* 2013; 28: 1975–1981
25. Noris M, Galbusera M, Gastoldi S *et al*. Dynamics of complement activation in atypical HUS and how to monitor eculizumab therapy. *Blood* 2014; 124: 1715–1726

CLINICAL KIDNEY JOURNAL
ckj