EXCEPTIONAL CASE

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

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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 peribital 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 m² by the 4-variable Modification
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/mm³ 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 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 g/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 m².

**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
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: a new classification. 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. Medjeriah-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-Abelada 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: 61–85
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. Allelic variants of complement genes associated with dense deposit disease and C3 glomerulonephritis. Kidney Int 2012; 71: 1559–1563
22. Radihakrishnan 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