Successful Treatment of Posttransplant Recurrent Complement C3 Glomerulopathy with Eculizumab

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Two-thirds of complement C3 glomerulopathy (C3G) recur after transplantation and commonly cause graft loss. There is not a standard treatment protocol for these cases. We present a kidney transplant patient with recurrent C3G who was successfully treated with eculizumab. Nephrotic proteinuria and hematuria occurred and creatinine levels increased after transplantation. A graft biopsy revealed recurrent C3G. The patient was administered 250 mg pulse methylprednisolone for 3 days and had 9 sessions of plasmapheresis. Since elevated creatinine levels and proteinuria persisted, eculizumab was instituted. A complete remission was observed after 9-month maintenance eculizumab treatment. Eculizumab may be a potentially effective option in kidney transplant patients with recurrent C3G unresponsive to other treatment modalities.

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Case Report

INTRODUCTION

Complement C3 glomerulopathy (C3G) is a disorder characterized by the presence of glomerular deposits composed of complement C3 and minimal immunoglobulin due to dysregulation of the alternative complement pathway.[1] Two-thirds of C3G cases recur after transplantation and commonly cause graft loss.[2] Because C3G is rarely seen in kidney transplant patients, there is not a standard treatment protocol for these cases. There is also little evidence with limited success from case reports to support the routine use of plasma therapy as a treatment modality in C3G.[3,4] Similarly, the data to support the successful use of anticellular immune suppression including steroid, mycophenolate mofetil (MMF), rituximab, and cyclophosphamide are inconclusive.[5] As evidence implicating complement dysregulation in C3G have accumulated, eculizumab, a monoclonal C5 antibody has been proposed as an anti-C5 therapy in C3G,[6] which has been reported to be successful in pediatric C3G cases.[7,8] Here, we present an adult kidney transplant patient diagnosed with C3G who was successfully treated with eculizumab with complete recovery of graft function.

CASE REPORT

A 53-year-old man without a history of a systemic disease was diagnosed with membranoproliferative glomerulonephritis on renal biopsy performed for proteinuria in 2013; immunofluorescence microscopy showing bright C3 and C1q in the mesangium and along glomerular capillary walls. The patient was initially given medical treatment consisting of MMF and steroids. However, MMF had to be discontinued due to its gastrointestinal side effects. Instead, intravenous cyclophosphamide, 750 mg/m^2, monthly for 3 doses was administered. In 2015, the patient presented with elevated serum creatinine and nephrotic-range proteinuria. A kidney biopsy revealed C3 glomerulopathy (Figure 1). Laboratory tests revealed a low serum C3 level (0.31 g/L; reference range, 0.79 g/L to 1.52 g/L) and normal serum C4 level. Serum C3

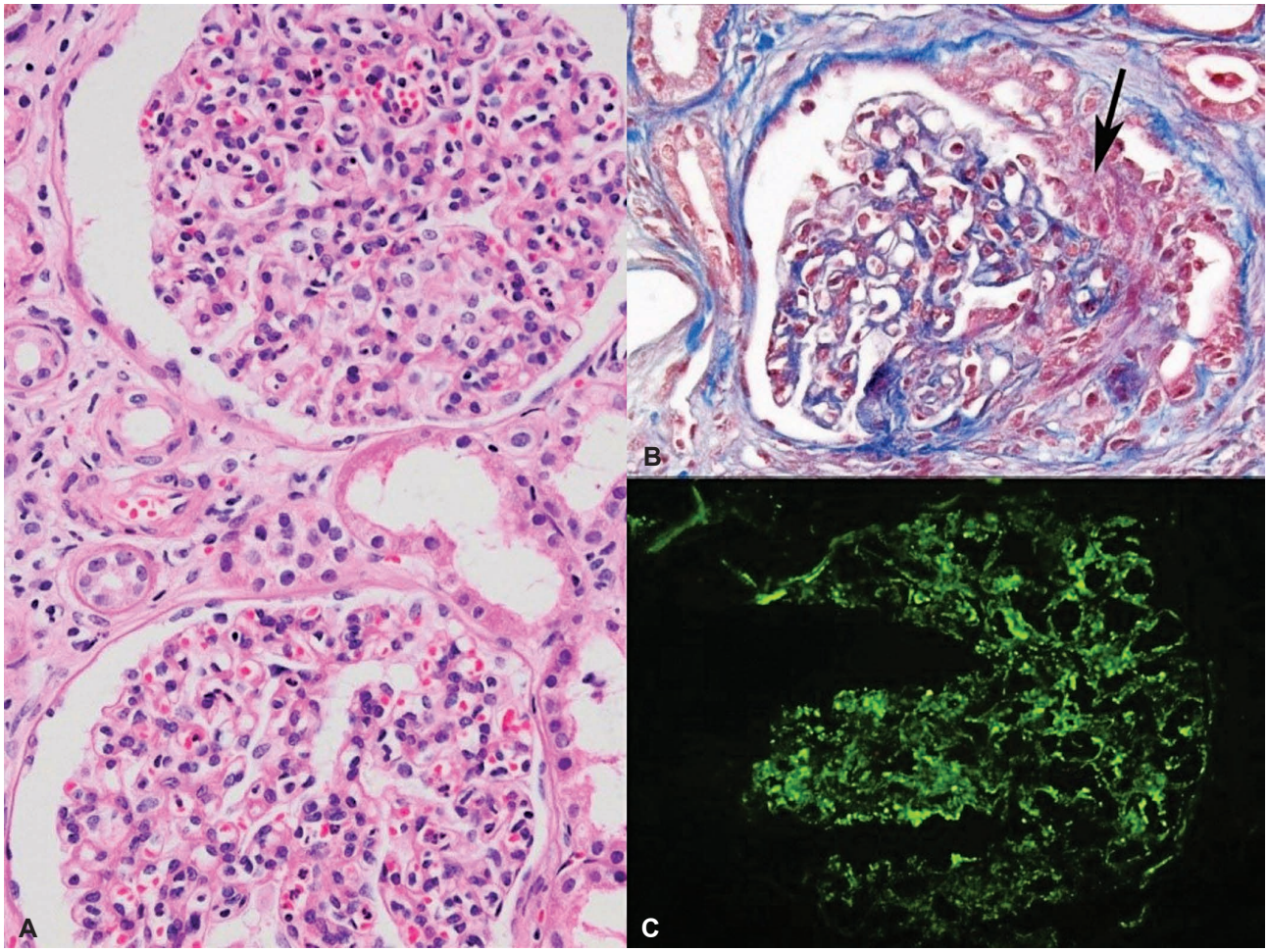

Figure 1. A. Diffuse endocapillary proliferation on light microscopy (hematoxylin-eosin, × 200). B, A glomerulus with a crescent formation (arrow) (Masson trichrome, × 200). C, Intense granular C3 deposition in a glomerulus, both mesangial and peripheral (immunofluorescence staining, anti-C3 Ab, × 200).

nephritic factor, terminal complement complex, factor H, and factor I levels and *CFH* mutation examinations were not performed.

The patient received a kidney from his wife in July 2016. Six months after kidney transplantation, he came for his routine follow-up visit with a complaint of leg and foot swelling. Laboratory tests revealed 24-hour urine protein of 3200 mg/d, hematuria, a creatinine level of 2.11 mg/dL, a blood urea nitrogen of 77 mg/dL, and a serum C3 level of 0.55 g/L. A graft biopsy showed the same changes as in the native kidney confirming the diagnosis of recurrent C3G in the transplanted kidney (Figure 2). The patient was treated with methylprednisolone, 250 mg, as an intravenous injection, once daily for 3 days, followed by 1 mg/kg/d, orally, and plasma exchange for a total of 9 sessions (3 sessions per week for 3 weeks). Since the patient did not respond to this treatment regimen, eculizumab therapy was instituted. Eculizumab was administered at 900 mg, intravenous, weekly, for induction for 4 weeks, followed by maintenance at 1200 mg every other week, with good tolerance and no adverse episodes related to the medication. The patient achieved complete remission after the 5th maintenance dose of eculizumab. After 10 months of maintenance treatment with eculizumab, the patient still had a normal graft function with a plasma creatinine level of 1.13 mg/dL and a 24-hour urine protein of 120 mg/d (Figure 3).

DISCUSSION

Recurrence rates of C3G can be as high as 66.7% after kidney transplantation.[9] Recently, few case reports have reported treatment with eculizumab in patients with C3G.[7,8] However, it has been mostly

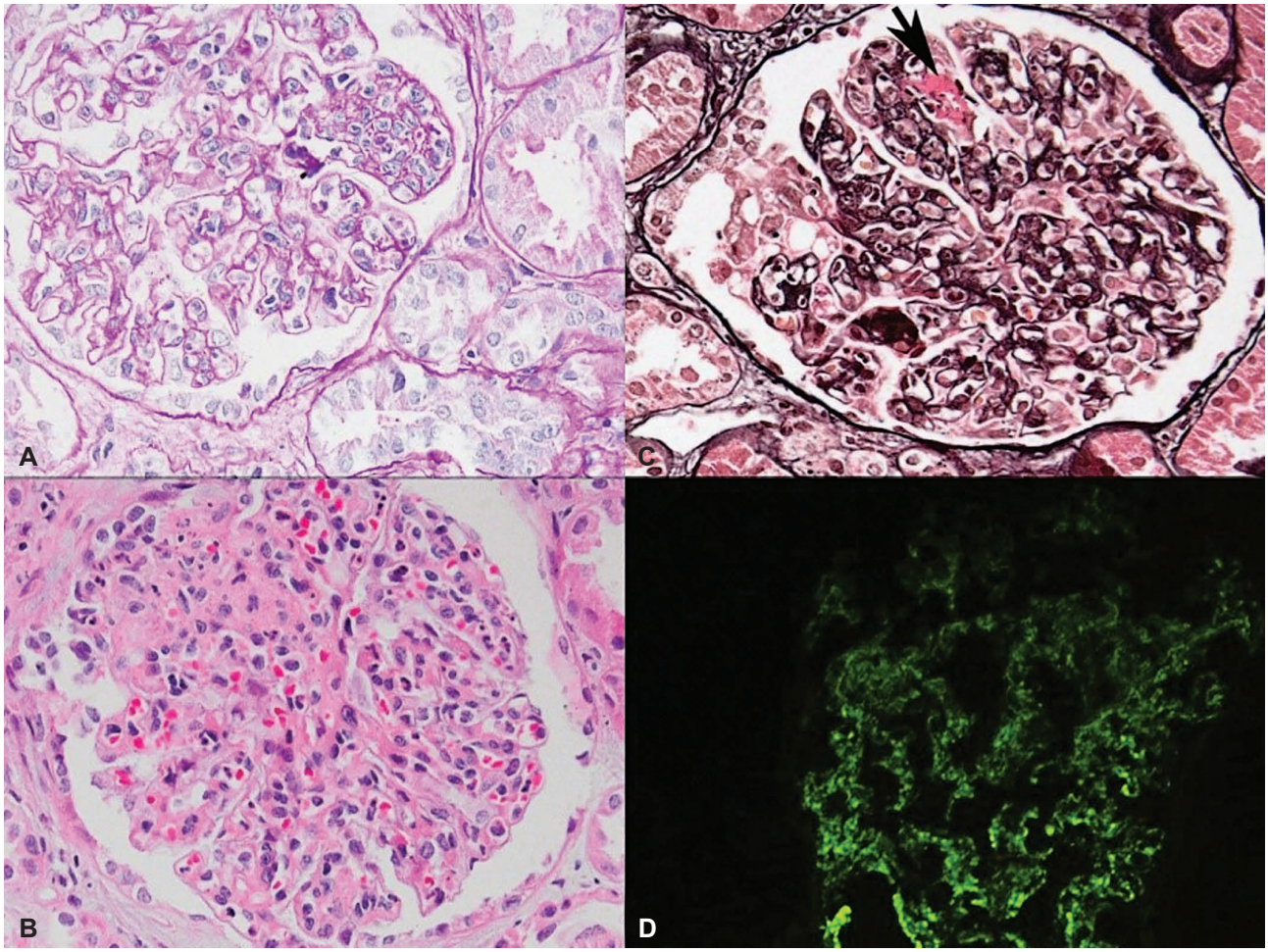

Figure 2. Recurrent glomerulonephritis in the renal allograft with endocapillary proliferation, focal fibrinoid necrosis (arrow in the panel C) and strong granular C3 staining in the glomeruli (A, periodic acid-Schiff, × 200; B, hematoxylin-eosin, × 200; C, Jones methenamine silver, × 200; D, immunofluorescence staining, anti-C3 Ab, × 200).

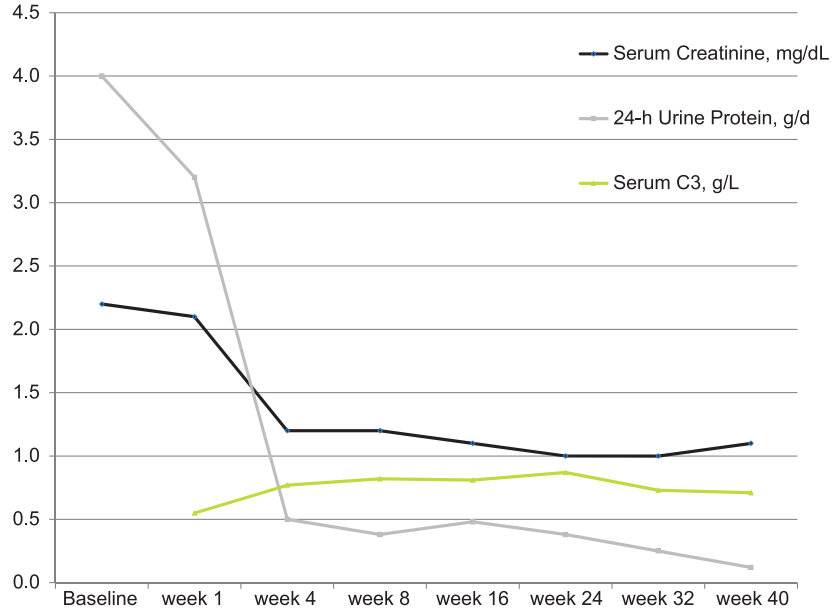

Figure 3. Biochemical parameters of the patient during eculizumab therapy. Eculizumab was administered, 900 mg, weekly for induction for 4 weeks followed by maintenance at 1200 mg every other week for a total period of 40 weeks.

utilized in pediatric cases and there is limited experience with eculizumab for treatment of recurrent C3G in adult kidney transplant patients.[8,10]

In the first report, Gurkan and colleagues described a 21-year-old white male who was diagnosed with dense deposit disease at the age of 8 years and suffered allograft recurrence of C3G. After 12 months of therapy with eculizumab, the patient achieved a partial remission. The authors noted that eculizumab blocked the membrane attack complex, but not the alternative complement pathway which resulted in partial control of the disease by the drug.[10] Secondly, McCaughan and colleagues reported the efficacy of eculizumab in a case of posttransplant recurrent C3G in a 29-year-old female patient. Thirteen weeks after transplantation, she was administered eculizumab which resulted in a marked clinical and biochemical response.[11] Finally, Bomback and coworkers treated 3 patients with dense deposit disease (1 with a kidney transplant) and 3 C3 glomerulonephritis patients (2 with a kidney transplant) with eculizumab for 12 months. Of the transplanted patients, 1 showed improvement in serum creatinine, 1 had partial remission of nephrotic syndrome, and 1 had stable laboratory values with less proliferation on repeat biopsy.[6] All of these reports noted at least partial response of recurrent C3G in kidney transplant patients. Data from these studies also suggest a long therapeutic trial of at least 6 months to assess response to eculizumab therapy.[6,10,11] In the present report, the patient achieved complete remission after the 5th maintenance dose and remained in remission during the 9 months of eculizumab therapy.

The most important serious adverse effect of eculizumab use is the infection risk with encapsulated organisms.[12] In the present report, we observed no undesirable effects or infections associated with the use of eculizumab. In conclusion, this report showed beneficial effects of eculizumab therapy in recurrent C3G.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Sethi S, Fervenza FC, Zhang Y, et al. C3 glomerulonephritis: clinicopathological findings, complement abnormalities, glomerular proteomic profile, treatment, and follow-up. Kidney Int. 2012;82:465-73.
2. Zand L, Lorenz EC, Cosio FG, et al. Clinical findings, pathology, and outcomes of C3GN after kidney transplantation. J Am Soc Nephrol. 2014;25:1110-17.
3. Servais A, Noël LH, Roumenina LT, et al. Acquired and genetic complement abnormalities play a critical role in dense deposit disease and other C3 glomerulopathies. Kidney Int. 2012;82:454-64.
4. Nester CM, Smith RJ. Treatment options for C3 glomerulopathy. Curr Opin Nephrol Hypertens. 2013;22:231-7.
5. Nester CM, Smith RJ. Diagnosis and treatment of C3 glomerulopathy. Clin Nephrol. 2013;80:395-403.
6. Bomback AS, Smith RJ, Barile GR, et al. Eculizumab for densedeposit disease and C3 glomerulonephritis. Clin J Am Soc Nephrol. 2012;7:748-56.
7. Daina E, Noris M, Remuzzi G. Eculizumab in a patient with dense-deposit disease. N Engl J Med. 2012;366:1161-3.
8. Lebraton C, Bacchetta J, Dijoud F, et al. C3 glomerulopathy and eculizumab: a report on four pediatric cases. Pediatr Nephrol. 2017;32:1023-8.
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. Gurkan S, Fyfe B, Weiss L, Xiao X, Zhang Y, Smith RJ. Eculizumab and recurrent C3 glomerulonephritis. Pediatr Nephrol. 2013;28:1975-81.
11. Mc Caughan JA, O'Rourke DM, Courtney AE. Recurrent dense deposit disease after renal transplantation: an emerging role for complementary therapies. Am J Transplant. 2012;12: 1046-51.
12. Brodsky RA, Young NS, Antonioli E, et al. Multicenter phase 3 study of the complement inhibitor eculizumab for the treatment of patients with paroxysmal nocturnal hemoglobinuria. Blood. 2008;111:1840-47.

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