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Long-term Eculizumab Therapy in a Child With Refractory Immune Complex–Mediated Membranoproliferative Glomerulonephritis

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INTRODUCTION

There have been recent developments in the understanding of the pathogenesis of membranoproliferative glomerulonephritis (MPGN) supporting a prominent role for the complement alternative pathway (AP).[1,2] MPGN due to AP dysregulation has been further classified into dense-deposit disease (DDD) and C3 glomerulonephritis (C3GN), and grouped together as C3 glomerulopathy (C3G). This entity includes all glomerular lesions that are characterized by predominant C3 accumulation with minimum or scant Ig deposition and highlights the pathogenetic contribution of complement.[1,2] On the other hand, MPGN secondary to autoimmune diseases or infections is labeled as immune complex–mediated MPGN.

C3G is associated with a poor prognosis, as 30% to 50% of patients progress to end-stage renal disease (ESRD) within 10 years of diagnosis, and around 50% have recurrence after transplantation.[1] Complement targeting therapy such as eculizumab has recently emerged as a novel therapeutic option for patients with C3G. There have been few case reports to describe the effectiveness of eculizumab in patients with C3G, but the literature is scarce in the pediatric population.[3-5] Moreover, there is very little insight into the long-term safety and efficacy regarding the use of eculizumab in immune complex–mediated MPGN. We present a child with refractory immune complex–mediated MPGN who was successfully treated with eculizumab for a period of 4 years.

Case Report

A 16-year-old girl presented with a 2-month history of edema, anemia, hypertension, microscopic hematuria, nephrotic range proteinuria, low C3 level, and was diagnosed as immune complex–mediated MPGN on renal biopsy (Figure 1). Treatment with prednisone and mycophenolate mofetil (MMF) was started (Table 1). Her detailed clinical picture has been published earlier.[4] Briefly, her proteinuria persisted and 4 months later, she was admitted with fever, pancytopenia, seizures, and pneumonia secondary to *Pseudomonas aeruginosa* sepsis. Her renal function worsened, and hemodialysis and plasmapheresis were initiated along with appropriate supportive treatment.

Interestingly, complement analysis revealed low C3, high soluble membrane attack complex (sMAC, sC5b-9) level (844 ng/ml; normal $<$ 320 ng/ml), low CH50, positive C3NeF, and absent CFHR 1 on western blot, interpreted as strong evidence for complement AP activation, possibly driven by a CFHR 1 deficiency and positive C3NeF. She received 9 sessions of plasmapheresis over a period of 11 days before commencing eculizumab. Initially, she received 4 doses of eculizumab (900 mg/wk for 4 weeks) followed by a rapid (i.e., within days) improvement in neurological

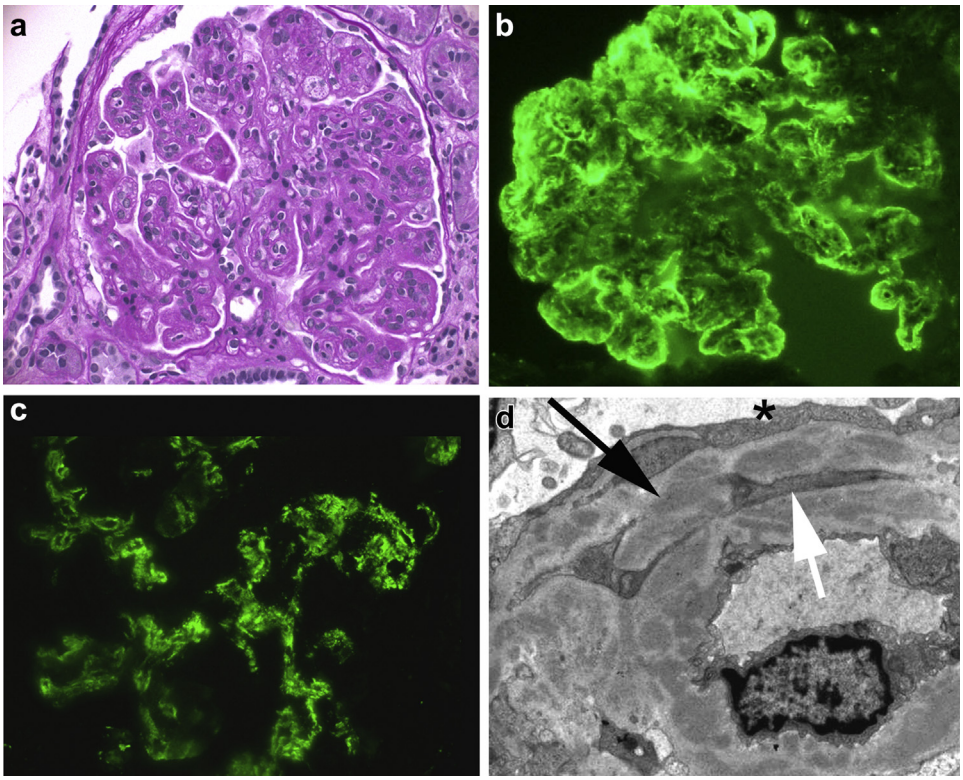

Figure 1. Histopathological features before receiving eculizumab. Biopsy findings pre-eculizumab. (a) Biopsy samples show a membranoproliferative appearance by light microscopy on periodic acid–Schiff staining. There is strong IgG staining (b) and less intense C3 staining (c). (d) By electron microscopy, there are subendothelial deposits (black arrow) and mesangial interposition (white arrow) with effacement of podocyte foot processes (*). Findings establish a diagnosis of immune complex–mediated membranoproliferative glomerulonephritis. (a–c, original magnification ×400; d, original magnification ×10,000.)

complications and hematological parameters. Hemodialysis was stopped after 2 weeks. After the sixth dose, her proteinuria had significantly improved (urine protein to creatinine ratio 0.04 mg/mg from a baseline of 3.89 mg/mg). Thereafter, she was maintained on biweekly eculizumab infusions of 1200 mg each. She did not have any side effects related to eculizumab. Prednisone was weaned and stopped over a period of 1 year after starting eculizumab. Figure 2 shows variation in the laboratory parameters from 3 months before until 48 months after initiating eculizumab.

Four years later, she continues to be on maintenance eculizumab (1200 mg every 2 weeks) without other immunosuppressive or antihypertensive medications. She has non–nephrotic-range proteinuria (urine protein-to-creatinine ratio at 51 months after eculizumab, 0.39 mg/mg). Her estimated glomerular filtration rate (eGFR) is 96.5 ml/min per 1.73 m^2, but she continues to have positive C3NeF (normal: negative), low C3, elevated C3d (86 mU/l; normal $<$ 40 mU/l), and elevated sMAC levels (606 ng/ml; normal $<$ 320 ng/ml).

DISCUSSION

MPGN is a rare, yet an important cause of glomerulopathy affecting children and young adults. The pathogenesis of MPGN may either be immune complex mediated or attributed to the defect in complement AP regulation, including mutations in the genes coding for C3[6] or complement inhibitors such as complement factor H (CFH), complement factor I (CFI), or membrane cofactor protein (MCP; CD46),[7] or the presence of C3NeF.[7,8] In this report, the patient was considered to be C3G based on obvious AP abnormalities, but her renal biopsy showed dominant staining of both Igs and C3. Acknowledging the strict histopathological criteria for C3G (i.e., dominant C3 staining $\leq$ 2 intensity levels above Ig staining), we continued to label her condition as immune complex–mediated MPGN.

There are no evidence-based guidelines for treatment in patients with C3G. Conventional therapies such as angiotensin-converting enzyme inhibitors, immunosuppressive agents and plasma exchange/infusions have been used but with variable results.[9–11] As activation of the complement AP is thought to be a major patho-mechanism in C3G, the use of complement-targeting and complement-control–restoring therapies such as eculizumab have evolved as an obvious treatment option (Table 2).

Eculizumab is a humanized anti-C5 monoclonal antibody that has been successfully used in patients with atypical hemolytic uremic syndrome. There is