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Exceptional Case

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Post-streptococcal glomerulonephritis associated with atypical hemolytic uremic syndrome: to treat or not to treat with eculizumab?

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Abstract

A 7-year-old male with poststreptococcal glomerulonephritis (PSGN) developed hemolytic uremic syndrome (HUS) and achieved remission. He was treated with eculizumab for 1 year. The eculizumab was discontinued and the patient remained in remission. This is the 10th reported case of PSGN associated with HUS. The histopathological feature observed at the 1-year follow-up was indistinguishable from the expected findings in an individual with healed PSGN without associated HUS. The relatively good prognosis in most prior cases and the absence of any reported recurrences strongly suggest that this form of atypical HUS does not warrant long-term eculizumab therapy.

Key words: aHUS, complement pathway, eculizumab, PSGN

Introduction

Hemolytic uremic syndrome (HUS) is defined by the triad of microangiopathic hemolytic anemia, thrombocytopenia and acute kidney injury, with ~90% of cases occurring following a diarrheal illness with Shiga-like toxin-producing bacteria. The remaining 10% of cases are grouped into the category of 'atypical' HUS (aHUS), which consists of a heterogeneous group of disorders with 50–60% of cases being associated with either genetic- or antibody-mediated complement dysregulation [1]. Importantly, a subset of children with the aHUS phenotype have a more favorable prognosis, may not have associated complement dysregulation and may not require treatment with plasmapheresis or anti-C5 antibody (eculizumab) [2, 3].

Post-streptococcal glomerulonephritis (PSGN) is the most common cause of glomerulonephritis in children, presenting ~1–3 weeks after streptococcal infection, and is usually associated with depressed C3 levels for up to 8 weeks [4]. In 1980, De Chadarevian *et al.* [5] first described the simultaneous occurrence of acute PSGN and HUS. There have been at least nine cases describing HUS associated with PSGN in the literature [5–12]. Importantly, these cases fall under the rubric of aHUS, as they are not associated with diarrhea or Shiga toxin exposure. Only three of these cases showed thrombotic microangiopathy on renal biopsy (Table 1) [8, 10, 11]. Furthermore, they are also associated with alternative complement pathway activation, suggesting a possible role for treatment with eculizumab.

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Table 1. Summary of biopsy findings and outcomes of patients with PSGN associated with aHUS

Author [ref.]	Patient age (years)/sex	Biopsy findings			Other comments	Outcome
		Light microscopy	Immunofluorescence	Electron microscopy		
De Chadarevian *et al.* [5]	5.5/male	Swollen glomeruli Widened capillary wall Capillary loops and extraglomerular arterioles with thrombi	Not reported	Subepithelial humps along glomerular basement membrane	Conservative management Prednisone which was weaned over 1 month	C3: normal at diagnosis *Creatinine*: normal within 3 weeks *Proteinuria*: decreased over 1 month *Blood pressure*: normal
Medani *et al.* [7]	13/male	Hypercellularity and proliferation of capillary endothelium involving all glomeruli No epithelial crescents	No sample obtained	Subepithelial deposits Mesangial and rare subendothelial deposits noted as well	On peritoneal dialysis for 7 days Conservative management	C3: normal (84 mg/dL) in 4 months *Creatinine*: improved to 1.2 mg/dL in 8 weeks *Blood pressure*: normal on follow-up
Proesmans *et al.* [12]	14/male	Proliferative mesangium No capillary thrombosis	Coarse C3 deposition in mesangium, extending along the capillary wall. Fine granules along the capillary wall IgM in segmental and less regular pattern	Electron-dense deposits along the basement membrane in the mesangium and in capillary loops	Conservative management	C3: normalized in 6 weeks *Creatinine*: 0.9 mg/dL at 12 months *Proteinuria*: 0.9 g/day at 12 months, 0.5 g/day at 3 years *Blood pressure*: antihypertensive medications were discontinued after 2 years
Siebels *et al.* [11]	26/male	Mesangial and endothelial cell proliferation Humped-shaped subendothelial deposits Arteriolar hyalinosis and extraglomerular thrombotic microangiopathy	Diffuse granular deposits of IgG, IgM, C3c and C3d along the basement membrane Irregular deposits of IgM, C1q, C3c, C3d and fibrin in some arteriolar walls	Subendothelial deposits (humps)	Conservative management	C3: not measured *Creatinine*: 1.15 mg/dL after 9 months *Proteinuria*: 0.15 g/day after 9 months
Tan *et al.* [10]	10/female	Hypercellular glomeruli Thickened glomerular capillary walls, often with double contours Capillary lumina with fresh thrombi and many glomeruli with thrombonecrotic lesions 60% crescent formation	C3 in all glomeruli, granular mesangial and capillary wall staining Fibrin, minor C1q and IgM in capillary walls	Subepithelial humped-shaped deposits Small subendothelial and mesangial deposits noted	Required hemodialysis Plasmapheresis with fresh frozen plasma	C3: normal in 2 months *Creatinine*: improved at 3 weeks, 1.1 mg/dL at 2 years *Proteinuria*: 1+ at 2-year follow-up *Blood pressure*: controlled on one antihypertensive medication

Table continues

Table 1. Continued

Author [ref.]	Patient age (years)/sex	Biopsy findings			Other comments	Outcome
		Light microscopy	Immunofluorescence	Electron microscopy		
Duvic *et al.* [8]	47/female	Eight glomeruli with mesangial and endothelial cell proliferation One small cellular crescent Three sclerotic glomeruli Arteries with subendothelial hyaline thrombi	Diffuse granular C3 and minor degree IgG and IgM in basement membrane Fibrin, minor C1q and IgM in capillary walls		Conservative management Fresh frozen plasma for 1 week	C3: normal in 3 months *Creatinine*: 1.5 mg/dL in 1 year *Proteinuria*: 0.3 g in 1 year *Blood pressure*: on ramipril and furosemide after 1 year
Laube *et al.* [9]	12/male	Extensive extra- and intracapillary proliferation No evidence of thrombotic microangiopathy	Not reported	Subendothelial humps Endothelial and mesangial cell proliferation	Hemodialysis for 2 weeks Six weeks of prednisolone Two weeks of daily enteral cyclophosphamide	C3: normal after 9 months *Creatinine*: 0.8 mg/dL after 2 years *Proteinuria*: 0.5 g/day after 2 years
Laube *et al.* [9]	6/female	Proliferation of mesangial cells Swelling of endothelial cells No evidence of thrombotic microangiopathy	C3 along the basement membrane, capillary walls and tubules	Subendothelial humps	Conservative management	C3: normal at 1 year *Creatinine*: normal (0.6 mg/dL) at 3 months *Proteinuria*: none at 3 months
Izumi *et al.* [6]	47/male	Endocapillary proliferation Two fibrocellular crescents present One glomeruli with global sclerosis	C3 along the capillary wall Ig negative, NAPlr positive	Many subendothelial humps Endothelial and mesangial cell proliferation	Fresh frozen plasma infusions for 10 days	C3: normal in 3 weeks *Proteinuria*: decreased to 1.02 g/day in 3 weeks
Current case	7/male	Acute diffuse glomerulonephritis 30% crescent formation	Granular IgG (1+) in mesangium C3 (2+) in mesangium and capillary loops	Subendothelial deposits	Treated with fresh frozen plasma followed by eculizumab	C3: normal in 4 months *Creatinine*: normal in 1 month *Proteinuria*: resolved in 1 month *Blood pressure*: on amlodipine for blood pressure control, was discontinued within one month of return of creatinine to baseline.

The use of eculizumab has revolutionized the treatment of complement-mediated diseases, including aHUS, paroxysmal nocturnal hematuria and C3 glomerulonephritis. Eculizumab blocks the complement pathway at the level of C5, preventing activation of the terminal pathway and formation of the membrane attack complex, thereby greatly improving outcomes among patients with complement-mediated aHUS.

This report describes the first case of PSGN-associated HUS in the posteculizumab era and discusses the rationale for considering treatment with eculizumab in such cases.

Case summary

Initial presentation

A 7-year-old male presented with 2 weeks of progressive facial edema, oligoanuria and 'iced-tea' colored urine. Three weeks prior he completed a course of amoxicillin followed by cefalexin for streptococcal throat infection. He had no history of bloody diarrhea or rash. Blood pressure was 136/87 mmHg. Physical examination revealed facial edema and bilateral lower extremity pitting edema. Urinalysis demonstrated 3+ protein and a large amount of blood with numerous red blood cell casts. Initial blood work demonstrated a creatinine of 6.4 mg/dL, potassium 7.2 mmol/L, albumin 3.3 g/dL, hemoglobin 11.7 g/dL, platelet count 70 000/μL, lactate dehydrogenase 1589 units/L, ASO titer >900 IU/mL, C3 20 mg/dL and C4 14.3 mg/dL. Owing to oliguric acute kidney injury with persistent hyperkalemia, fluid overload and hypertension, he was started on continuous veno-venous hemodiafiltration (CVVHDF) and underwent a renal biopsy (Figures 1 and 2).

Pathology

Light microscopy

Glomeruli showed moderate to marked endocapillary proliferation with numerous neutrophils within capillary spaces. About 30% of glomeruli demonstrated early cellular crescent formation. No fibrin thrombi were identified.

Immunofluorescence

Immunofluorescence revealed 1+ granular IgG staining (primarily in the mesangium) and 2+ granular C3 staining (in the mesangium and capillary loops).

Electron microscopy

Subepithelial and more numerous intramembranous and mesangial electron-dense deposits were observed on electron microscopy.

Clinical course

The patient remained on CVVHDF for 48 h. Although his thrombocytopenia initally resolved by day 5, he was noted to have a mild drop in his hemoglobin (10.6 g/dl) from day 2 of admission. In response to his dialysis dependence and crescentic glomerulonephritis, he was treated with intravenous methylprednisolone 250 mg for 3 days and subsequently treated with oral prednisone for 1 week and discharged home on antihypertensive therapy after 7 days. His anemia persisted, although his platelet counts remained normal. The prednisone was discontinued at that time after he presented to the clinic with hypertensive urgency, which quickly resolved.

One week after the prednisone was discontinued, his blood pressure, edema and renal function (creatinine 0.8 mg/dL) all continued to improve; however, a complete blood count revealed a hemoglobin of 7.1 g/dL, platelet count of 97 000/μL and an elevated lactate dehydrogenase of 866 units/L. He subsequently had an episode of epistaxis and was noted to have a further drop in his hemoglobin to 6.6 g/dL with a reticulocyte count of 4.9% and schistocytes on peripheral smear. Evaluation for aHUS revealed normal factor H and I levels, undetectable factor H autoantibodies and the absence of C3 nephritic factor. A slightly low factor B (9.7 mg/dL) was noted, suggesting consumption through activation of the alternate complement pathway. No identified mutations in complement factor H, complement factor I, complement factor B, membrane cofactor protein, diacylglycerol kinase-epsilon, C3, thrombomodulin or complement factor H–related protein 1/3/5 genes were detected.

He was treated with fresh frozen plasma, but he developed an allergic reaction after his second dose. Given that only ~10% of patients with aHUS have anti-factor H antibodies, which respond to plasma exchange alone without plasma infusions, we elected to treat with eculizumab. He subsequently received the meningococcal vaccine, penicillin prophylaxis and was given intravenous eculizumab 600 mg. One week later, his creatinine was stable at 0.8 mg/dL, hemoglobin was 9.6 g/dL and platelet count improved to 405 000/μL. He received three weekly doses of eculizumab followed by doses every 2 weeks.

At the 1-month follow-up he had normal renal function (creatinine 0.5 mg/dL), no proteinuria and no hypertension. His hemoglobin and platelet count normalized. His complement levels were rechecked 4 months after initial presentation and had returned to normal (C3, 108 mg/dL; C4, 35 mg/dL).

He was treated for ~1 year with eculizumab and remained in complete remission. A repeat biopsy was performed at that time to help inform future treatment decisions.

Pathology

Light microscopy

Approximately 25% of the glomeruli were globally sclerotic. The remaining glomeruli were essentially normal with thin and delicate capillary membranes, patent capillary lumens and a minimal to mild increase in mesangial cells and matrix.

Immunofluorescence

Immunofluorescence revealed 1+ C3 deposition involving 40% of the glomeruli in a patchy, granular mesangial distribution.

Electron microscopy

Small, scattered predominantly intramembranous electron-dense deposits were noted on electron microscopy.

Clinical course

After the biopsy, eculizumab was discontinued and the patient has remained without relapse for the last 6 months.

Discussion

PSGN-associated HUS has rarely been described, with this patient being the 10th case reported. This case is unique in two respects. First, we describe the course and management of the first patient with PSGN-associated HUS in the era of eculizumab. Furthermore, our patient is the also first to have undergone a repeat biopsy after a prolonged period of remission. In general, the prognosis of PSGN-associated HUS has been favorable, with the majority of patients recovering fully or having mild residual chronic kidney disease or proteinuria [5–12]. Varying treatment regimens, unclear pathophysiology and short follow-up periods (Table 1) limit the current understanding of this association.

Clinical Kidney Journal

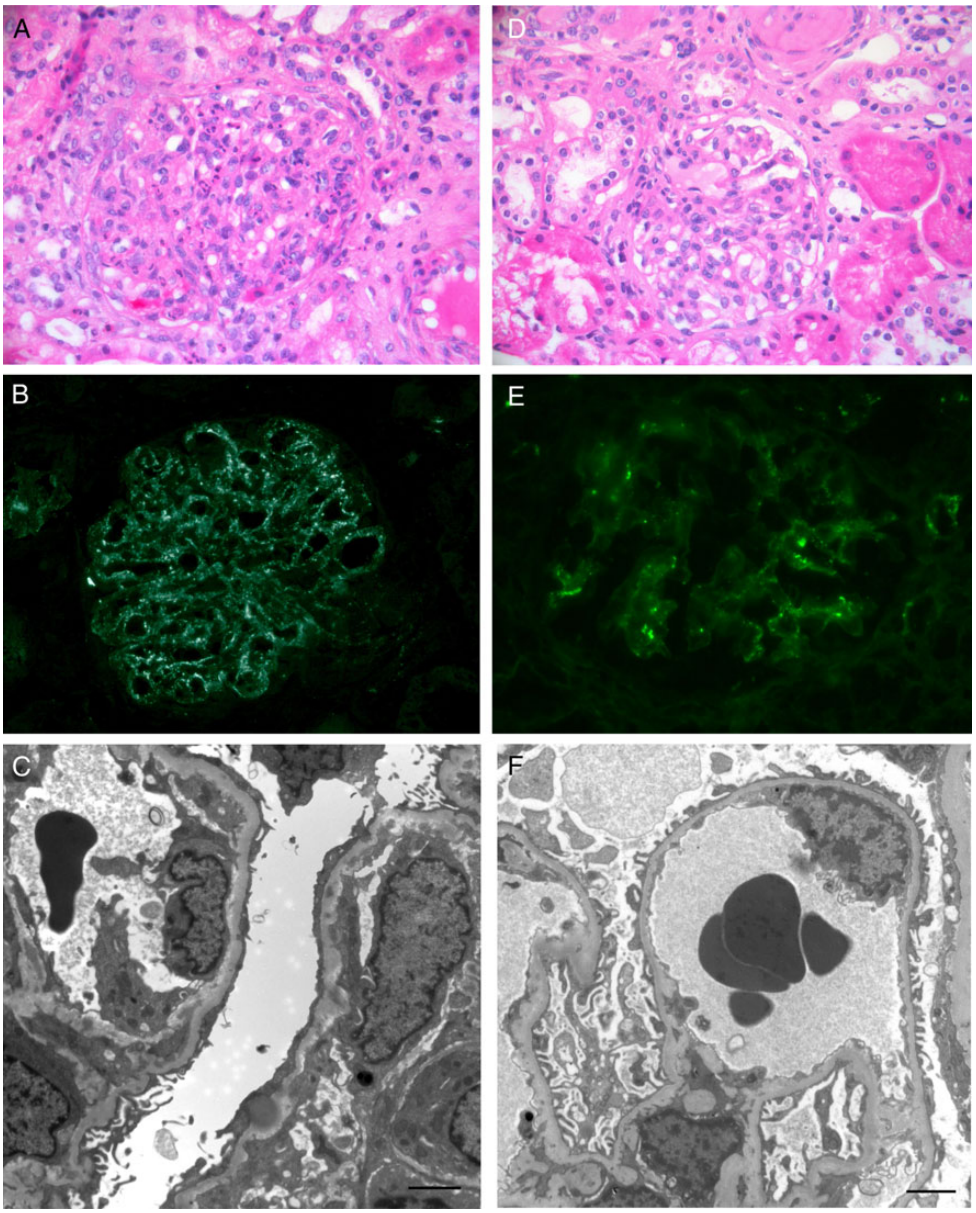

Fig. 1. (**A**) Light microscopy (hematoxylin and eosin, ×400 original magnification), (**B**) immunofluorescence microscopy (C3, ×400 original magnification), (**C**) electron microscopy (scale bar = 2 μm), (**D**) light microscopy (hematoxylin and eosin, ×400 original magnification), (**E**) immunofluorescence microscopy (C3, ×400 original magnification), (**F**) electron microscopy (scale bar = 2 μm). (A) Glomerulus from the first biopsy showing a proliferative, exudative glomerulonephritis with endocapillary and mesangial cell proliferation and a neutrophilic infiltrate. (B) Immunofluorescence for C3 with coarse granular staining within capillary loops and mesangium; IgG had a similar pattern but was less intense. (C) Electron microscopy with subepithelial electron-dense 'humps'. (D) Subsequent biopsy showing residual mesangial hypercellularity; (E) globally sclerotic glomeruli (upper center) were also present as well as scant C3 deposits in a subset of glomeruli; IgG was absent. (F) Small, primarily intramembranous residual deposits.

This ambiguity is highlighted by the observation that three of the patients previously described were treated with either plasmapheresis or plasma infusions [5, 8, 10], and five were treated with conservative management alone [6, 7, 9, 11, 12].

The alternative complement pathway is constitutively active and is under tight modulation by regulatory proteins. Genetic mutations in the factors that regulate the alternative pathway can be disease-causing [13]. Mutations in the factor H gene have been described in patients with aHUS as well as C3 glomerulonephritis. Interestingly, the histological characteristics of PSGN can be indistinguishable from C3 glomerulonephritis. However, on immunofluorescence, biopsies of patients with C3 glomerulonephritis show isolated C3 staining and are immunoglobulin negative [13]. Our patient presented with clinical and histological features of PSGN as well as anemia and thrombocytopenia consistent with aHUS. Given that these diseases are both mediated via the alternate complement pathway, it is tempting to speculate that blockade of the terminal complement pathway through the use of eculizumab might improve outcomes.

The typical histopathological findings noted in PSGN include diffuse hypercellularity of the endothelial and mesangial cells, infiltration of the glomeruli with polymorphonuclear cells and obliteration of the capillary lumens [4, 14]. Immunofluorescence demonstrates granular deposits of IgG and C3 along the capillary loops and in the mesangium [15]. The ultrastructural finding of subepithelial humps, from deposits located between glomerular capillary basement membrane and the epithelial, was first described by Kimmelstiel *et al.* [16]; however, it is now recognized

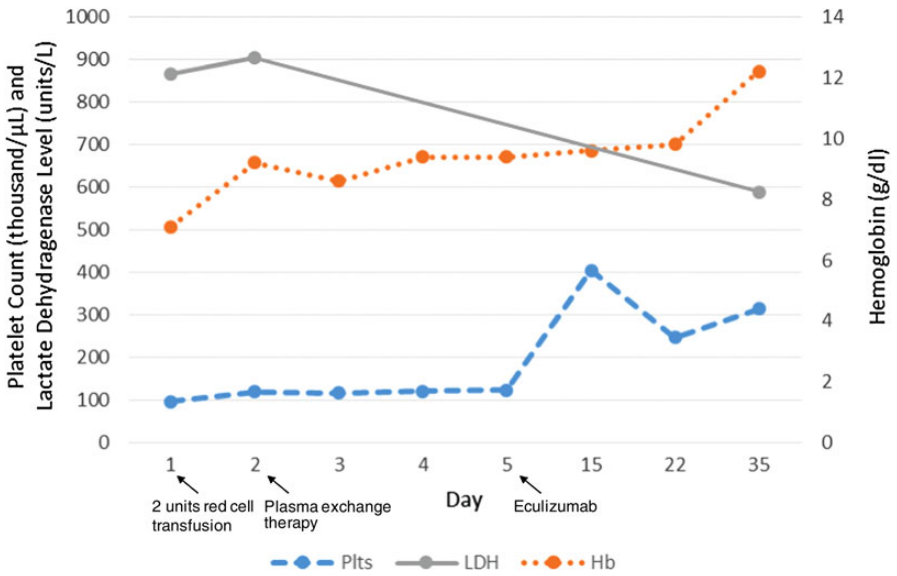

Fig. 2. Graph demonstrating the improvement in platelet count, hemoglobin and lactate dehydrogenase levels after plasma exchange therapy and subsequently starting eculizumab.

that the deposits may be found in subendothelial and intramembranous locations [17].

In healing PSGN, it has been suggested that resolution of subepithelial deposits occurs either by gradual dissolution and passage into the epithelial cytoplasm or by a second route, where larger portions of the deposits are removed by epithelial endocytotic activity [18]. Persistent ultrastructural and immunofluorescence changes have been noted after acute disease, even with clinical recovery or when light microscopy revealed healing [19–21]. In a review of 17 biopsies from five patients with PSGN at a mean follow-up of 2.8 years, Törnroth [18] demonstrated that after 45 days from the onset of PSGN, the subepithelial electron dense deposits were most often in the process of resolving, and many transformed into intramembranous deposits that seemed to persist. In a retrospective review of 1012 consecutive biopsy specimens, Haas [22] found 57 cases of incidental or presumed healed PSGN. Importantly, >90% demonstrated persistent glomerular immune deposits consisting of C3.

The histopathological findings in our patient are indistinguishable from prior reports of 'apparently healed' PSGN [18, 22, 23] without features of HUS. This strongly suggests that this form of aHUS does not merit long-term eculizumab therapy and is extremely unlikely to recur. This is supported by the absence of any prior reports of recurrence in the literature. The question as to whether eculizumab confers any potential benefit in the short term is less clear. Temporally, the hematological parameters in our patient seemed to improve soon after treatment was initiated; however, none of the prior cases in the literature experienced any long-term hematological issues, suggesting that supportive management can be a reasonable alternative. Additionally, although our patient had continued improvement of renal function after the eculizumab was initiated, the patient had already improved substantially prior to the therapy.

Conflict of interest statement

None declared.

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