EXCEPTIONAL CASE

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

Table 1. Summary of biopsy findings and outcomes of patients with PSGN associated with aHUS
<table>
<thead>
<tr>
<th>Author [ref.]</th>
<th>Patient age (years)/sex</th>
<th>Biopsy findings</th>
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<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duvic et al. [8]</td>
<td>47/female</td>
<td>Eight glomeruli with mesangial and endothelial cell proliferation</td>
<td>Diffuse granular C3 and minor degree IgG and IgM in basement membrane</td>
<td>Three sclerotic glomeruli</td>
<td>Conservative management</td>
<td>C3: normal in 3 months</td>
<td></td>
</tr>
<tr>
<td>Laube et al. [9]</td>
<td>12/male</td>
<td>Extensive extra- and intracapillary proliferation</td>
<td>Not reported</td>
<td>Subendothelial humps</td>
<td>Hemodialysis for 2 weeks</td>
<td>C3: normal after 9 months</td>
<td></td>
</tr>
<tr>
<td>Laube et al. [9]</td>
<td>6/female</td>
<td>Proliferation of mesangial cells</td>
<td>C3 along the basement membrane, capillary walls and tubules</td>
<td>Subendothelial humps</td>
<td>Conservative management</td>
<td>C3: normal at 1 year</td>
<td></td>
</tr>
<tr>
<td>Izumi et al. [6]</td>
<td>47/male</td>
<td>Endocapillary proliferation Two fibrocellular crescents present</td>
<td>C3 along the capillary wall Ig negative, NAPiR positive</td>
<td>Many subendothelial humps</td>
<td>Fresh frozen plasma infusions for 10 days</td>
<td>C3: normal in 3 weeks</td>
<td></td>
</tr>
<tr>
<td>Current case</td>
<td>7/male</td>
<td>Acute diffuse glomerulonephritis 30% crescent formation</td>
<td>Granular IgG (1+) in mesangium C3 (2+) in mesangium and capillary loops</td>
<td>Subendothelial deposits</td>
<td>Treated with fresh frozen plasma followed by eculizumab</td>
<td>C3: normal in 4 months</td>
<td></td>
</tr>
</tbody>
</table>

**Other comments:****
- Duvic et al. [8]: Fresh frozen plasma for 1 week
- Duvic et al. [8]: C3: normal in 3 months
- Laube et al. [9]: C3: normal after 9 months
- Izumi et al. [6]: C3: normal in 3 weeks
- Current case: C3: normal in 4 months

**Outcome:**
- Conservative management
- Hemodialysis for 2 weeks
- Hemodialysis for 2 weeks
- Conservative management
- Fresh frozen plasma infusions for 10 days
- Treated with fresh frozen plasma followed by eculizumab

**Medical conditions:**
- Mesangial and endothelial cell proliferation
- Three sclerotic glomeruli
- Subendothelial hyaline thrombi
- Endothelial and mesangial cell proliferation
- Subendothelial humps
The use of eculizumab has revolutionized the treatment of complement-mediated diseases, including aHUS, paroxysmal nocturnal hemoglobinuria 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 initially 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.
This ambiguity is highlighted by the observation that three of the patients previously described were treated with either plasmaapheresis 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...
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.

References