Pneumococcal hemolytic uremic syndrome and steroid resistant nephrotic syndrome

Andrew P. Groves
Washington University School of Medicine

Patrick Reich
Washington University School of Medicine

Binayak Sigdel
Washington University School of Medicine

T. Keefe Davis
Washington University School of Medicine

Follow this and additional works at: https://digitalcommons.wustl.edu/open_access_pubs

Recommended Citation
Groves, Andrew P.; Reich, Patrick; Sigdel, Binayak; and Davis, T. Keefe, "Pneumococcal hemolytic uremic syndrome and steroid resistant nephrotic syndrome." Clinical Kidney Journal. 9,4. 572-575. (2016). https://digitalcommons.wustl.edu/open_access_pubs/5162

This Open Access Publication is brought to you for free and open access by Digital Commons@Becker. It has been accepted for inclusion in Open Access Publications by an authorized administrator of Digital Commons@Becker. For more information, please contact vanam@wustl.edu.
Pneumococcal hemolytic uremic syndrome and steroid resistant nephrotic syndrome

Andrew P. Groves1, Patrick Reich2, Binayak Sigdel3 and T. Keefe Davis4

1Washington University School of Medicine, St Louis, MO, USA, 2Division of Infectious Disease, Department of Pediatrics, Washington University School of Medicine, St Louis, MO, USA, 3Division of Critical Care Medicine, Department of Pediatrics, Washington University School of Medicine, St Louis, MO, USA and 4Division of Nephrology, Department of Pediatrics, Washington University School of Medicine, St Louis, MO, USA

Correspondence to: T. Keefe Davis; E-mail: davis_tk@kids.wustl.edu

Abstract

Pneumococcal-associated hemolytic uremic syndrome (pHUS) is a rare but severe complication of invasive Streptococcus pneumoniae infection. We report the case of a 12-year-old female with steroid-resistant nephrotic syndrome treated with adrenocorticotrophic hormone (H.P. Acthar® Gel), who developed pneumococcal pneumonia and subsequent pHUS. While nephrotic syndrome is a well-known risk factor for invasive pneumococcal disease, this is the first reported case of pHUS in an adolescent patient with nephrotic syndrome, and reveals novel challenges in the diagnosis, treatment and potential prevention of this complication.

Key words: Acthar, hemolytic, nephrotic, streptococcus, uremic

Background

Hemolytic uremic syndrome (HUS) is characterized by the triad of microangiopathic hemolytic anemia, thrombocytopenia and acute renal failure. HUS in children is most commonly caused by Shiga-like toxin-producing Escherichia coli (STEC), with pneumococcal-associated HUS (pHUS) accounting for 5% of acquired cases. Most cases occur in neonates and children <2 years of age. The clinical course and overall outcomes of pHUS are severe. Up to 85% of patients require dialysis with a mortality rate of >10% [1, 2]. The inciting event is endothelial damage activating a microangiopathic cascade of thrombotic vascular injury. Streptococcus pneumoniae cleaves N-acetylneuraminic acid (sialic acid) and exposes the Thomsen–Friedenreich antigen (T-antigen) on glomerular endothelial cell glycoproteins [3]. This process, known as T-activation, then leads to IgM binding from circulating IgM anti-T antibodies, and the clinical syndrome of HUS (Figure 1) [4].

Treatment of pHUS is with antibiotics with activity against S. pneumoniae and supportive care. If necessary, transfusion of washed blood products is preferable to avoid increasing the levels of preformed anti-T antibodies, which are high in unwashed products. Anecdotal evidence supports the use of plasma exchange with 5% albumin replacement, and avoiding fresh frozen plasma (FFP) due to preformed anti-T antibodies in the pooled product [5–7].

Case report

A 12-year-old female with steroid-resistant nephrotic syndrome presented to the emergency department with fever, shortness of breath and cough. On exam she was tachycardic and tachypneic, requiring 3 L of supplemental oxygen. She was given 1 L of normal saline bolus intravenously. A chest X-ray identified bilateral pulmonary edema. She met criteria for sepsis [8]. She was started...
on vancomycin and cefotaxime, and admitted to our pediatric intensive care unit for further management. Past medical history was remarkable for the diagnosis of nephrotic syndrome at the age of 5 years. Although initially responsive to steroids she suffered several relapses when the steroid dose was tapered. At the age of 6 years a renal biopsy showed findings consistent with minimal change disease. Genetic testing for inherited nephrotic syndromes identified a heterozygous, non-coding mutation in the transient receptor potential cation channel subfamily C member 6 (TRPC6) gene without clinical significance. She was given an 8-week course of cyclophosphamide, which induced a 1.5-year remission. After relapse and a failed attempt to induce full remission with oral steroids she was started on tacrolimus. Over the next 3 years she had a partial clinical response, with improved edema but persistent proteinuria. Out of concern for missed focal segmental glomerulosclerosis (FSGS) and long-term calcineurin inhibitor nephrotoxicity, a repeat biopsy was performed. Biopsy showed interstitial nephritis without evidence of FSGS. Due to drug-resistant nephrotic syndrome and biopsy findings suggesting possible drug injury she was started on a trial of adrenocorticotrophic hormone (H.P. Acthar® Gel; Mallinckrodt Pharmaceuticals, St Louis, MO, USA) twice weekly in addition to tacrolimus. She received Acthar® for 2 months prior to presentation.

In the intensive care unit
An initial blood culture grew out S. pneumoniae at 8 h, and a nasopharyngeal swab PCR was positive for parainfluenza type 2. Overnight the patient developed oliguria, the creatinine increased from 1.4 to 2.4 mg/dL, and the hemoglobin decreased from 11.4 to 7.4 g/dL (Table 1). Acthar® and tacrolimus were discontinued. She was transfused one unit of unwashed packed red blood cells (pRBCs) and started on continuous veno-venous hemofiltration due to worsening kidney function and pulmonary edema. On hospital day 4 she developed respiratory failure requiring intubation. A computed tomography scan of the chest demonstrated bilateral patchy consolidation consistent with bronchopneumonia, and bilateral pleural effusions. High-dose hydrocortisone was administered due to concern for adrenal suppression from chronic steroid/Acthar® administration. The platelet count continued to decrease and her clinical condition worsened, requiring

### Table 1. Pertinent laboratory data

<table>
<thead>
<tr>
<th>Laboratory test</th>
<th>Admission (Day 1)</th>
<th>After PLEX (Day 8)</th>
<th>Day 25</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>7.4</td>
<td>8.6</td>
<td>10.1</td>
<td>12.1–15.1</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>22.6</td>
<td>26.4</td>
<td>29.5</td>
<td>36.1–44.3</td>
</tr>
<tr>
<td>Platelet count (×109/L)</td>
<td>100</td>
<td>81</td>
<td>225</td>
<td>140–440</td>
</tr>
<tr>
<td>Lactate dehydrogenase (U/L)</td>
<td>294</td>
<td>NA</td>
<td>NA</td>
<td>100–250</td>
</tr>
<tr>
<td>Bilirubin (mg/dL)</td>
<td>0.1</td>
<td>0.9</td>
<td>0.9</td>
<td>0–0.4</td>
</tr>
<tr>
<td>Blood urea nitrogen (mg/dL)</td>
<td>30</td>
<td>10</td>
<td>50</td>
<td>9.0–18.0</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>1.4</td>
<td>1.9</td>
<td>8</td>
<td>0.2–0.8</td>
</tr>
<tr>
<td>Fibrinogen (mg/dL)</td>
<td>737</td>
<td>426</td>
<td>NA</td>
<td>177–401</td>
</tr>
<tr>
<td>PT/aPTT (in seconds)</td>
<td>19.4/48.6</td>
<td>21.1/43.9</td>
<td>NA</td>
<td>12–16.1/23–40.6</td>
</tr>
<tr>
<td>DCT</td>
<td>NA</td>
<td>Negative</td>
<td>NA</td>
<td>Negative</td>
</tr>
<tr>
<td>ADAMST13</td>
<td>72%</td>
<td>Negative</td>
<td>Positive</td>
<td>70%</td>
</tr>
<tr>
<td>Smear (Schistocytes)</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
<td>Negative</td>
</tr>
</tbody>
</table>

ADAMST13, a disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13; DCT, direct Coombs test; NA, not available/not obtained; PLEX, plasma exchange; PT/aPTT, prothrombin time/activated partial thromboplastin time.
in particular is a major cause of sepsis and peritonitis in
ary effects of cytotoxic therapies [19
loss of immunoglobulins and complement factors, and second-
Nephrotic syndrome is a well-known cause of secondary im-
maly a risk factor for development of pHUS at an older age.

One unique aspect of this case was the patient
creasing to end-stage renal disease, and 16% with chronic kidney

The clinical course of pHUS is typically more severe than
diarrheal HUS, with more frequent need for dialysis and transfu-

Another potential risk factor in this patient was her exposure
to immunosuppressive agents. Tacrolimus has a well-known
association with HUS, but does not typically cause a positive
Coombs test. Also, in a review of 16 cases of tacrolimus-induced
HUS, the average time from initiating tacrolimus to disease onset
was 7.1 months, while our patient had been treated for over 3
years [23]. In addition to tacrolimus, our patient was started
with supportive care, antibiotics and temporary kidney replace-
ment therapy (KRT), the patient slowly recovered. She was even-
tually discharged home on hospital day 39, her creatinine having

Table 2. Pneumococcal immunization recommendations in nephrotic syndrome

<table>
<thead>
<tr>
<th>Patients who have NOT previously received PPSV23</th>
<th>PCV13</th>
<th>PPSV23</th>
<th>PPSV23</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 dose</td>
<td>1st dose ≥8 weeks after PCV13 dose</td>
<td>2nd dose ≥5 years after 1st PPSV23 dose</td>
<td></td>
</tr>
<tr>
<td>Patients who have previously received PPSV23</td>
<td>1 dose ≥8 weeks after last PPSV23 dose</td>
<td>N/A—already received 1st dose</td>
<td></td>
</tr>
</tbody>
</table>

ACIP, Advisory Committee on Immunization Practices; PCV13, 13-valent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine.
	nephrotic syndrome [22], yet this is the first reported case of
pHUS in a patient with nephrotic syndrome.

Diagnosis of pHUS is based on the association of the clinical triad
of HUS with confirmed or suspected S. pneumoniae infection [11].
Evidence of T-antigen exposure (direct Coombs test, polyaggluti-
nation test or peanut lectin agglutination test) can help support
the diagnosis, but is not mandatory [12]. The patient met diag-
nostic criteria for pHUS, and additionally had a positive direct
Coombs test (Table 1). While disseminated intravascular coagu-
ation (DIC) with multiorgan failure was considered as an alterna-
tive diagnosis, it was eventually rejected due to evidence of
autoimmune hemolysis (schistocytes, positive Coombs), and
normal fibrinogen level. Initially the mildly prolonged prothrom-
bin time/activated partial thromboplastin time (PT/APTT) hinted
toward the possibility of DIC, but coagulation abnormalities are
common in pHUS, and DIC is typically not considered without
significant PT/APTT elongation along with decreased fibrinogen.

One unique aspect of this case was the patient’s age and risk
factors. The median age of pHUS reported in the literature ranges
from 13 to 24 months [1, 13, 14]. Four cases of pHUS in adults have
been reported [15–18]. Two of these patients had undergone
splenectomy, and so underlying immunodeficiency is presum-
ably a risk factor for development of pHUS at an older age.
Nephrotic syndrome is a well-known cause of secondary im-
munodeficiency due to multiple factors including edema, urinary
loss of immunoglobulins and complement factors, and second-
ary effects of cytotoxic therapies [19–21]. Streptococcus pneumoniae
in particular is a major cause of sepsis and peritonitis in

Discussion

Diagnosis of pHUS is based on the association of the clinical triad
of HUS with confirmed or suspected S. pneumoniae infection [11].
Evidence of T-antigen exposure (direct Coombs test, polyaggluti-
nation test or peanut lectin agglutination test) can help support
the diagnosis, but is not mandatory [12]. The patient met diag-
nostic criteria for pHUS, and additionally had a positive direct
Coombs test (Table 1). While disseminated intravascular coagu-
ation (DIC) with multiorgan failure was considered as an alterna-
tive diagnosis, it was eventually rejected due to evidence of
autoimmune hemolysis (schistocytes, positive Coombs), and
normal fibrinogen level. Initially the mildly prolonged prothrom-
bin time/activated partial thromboplastin time (PT/APTT) hinted
toward the possibility of DIC, but coagulation abnormalities are
common in pHUS, and DIC is typically not considered without
significant PT/APTT elongation along with decreased fibrinogen.

One unique aspect of this case was the patient’s age and risk
factors. The median age of pHUS reported in the literature ranges
from 13 to 24 months [1, 13, 14]. Four cases of pHUS in adults have
been reported [15–18]. Two of these patients had undergone
splenectomy, and so underlying immunodeficiency is presum-
ably a risk factor for development of pHUS at an older age.
Nephrotic syndrome is a well-known cause of secondary im-
munodeficiency due to multiple factors including edema, urinary
loss of immunoglobulins and complement factors, and second-
ary effects of cytotoxic therapies [19–21]. Streptococcus pneumoniae
in particular is a major cause of sepsis and peritonitis in

hypersplenism, and so underlying immunodeficiency is presum-
ably a risk factor for development of pHUS at an older age.
Nephrotic syndrome is a well-known cause of secondary im-
munodeficiency due to multiple factors including edema, urinary
loss of immunoglobulins and complement factors, and second-
ary effects of cytotoxic therapies [19–21]. Streptococcus pneumoniae
in particular is a major cause of sepsis and peritonitis in
nephrotic syndrome [22], yet this is the first reported case of
pHUS in a patient with nephrotic syndrome.

Another potential risk factor in this patient was her exposure
to immunosuppressive agents. Tacrolimus has a well-known
association with HUS, but does not typically cause a positive
Coombs test. Also, in a review of 16 cases of tacrolimus-induced
HUS, the average time from initiating tacrolimus to disease onset
was 7.1 months, while our patient had been treated for over 3
years [23]. In addition to tacrolimus, our patient was started
with supportive care, antibiotics and temporary kidney replace-
ment therapy (KRT), the patient slowly recovered. She was even-
tually discharged home on hospital day 39, her creatinine having

Table 2. Pneumococcal immunization recommendations in nephrotic syndrome

<table>
<thead>
<tr>
<th>Patients who have NOT previously received PPSV23</th>
<th>PCV13</th>
<th>PPSV23</th>
<th>PPSV23</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 dose</td>
<td>1st dose ≥8 weeks after PCV13 dose</td>
<td>2nd dose ≥5 years after 1st PPSV23 dose</td>
<td></td>
</tr>
<tr>
<td>Patients who have previously received PPSV23</td>
<td>1 dose ≥8 weeks after last PPSV23 dose</td>
<td>N/A—already received 1st dose</td>
<td></td>
</tr>
</tbody>
</table>

ACIP, Advisory Committee on Immunization Practices; PCV13, 13-valent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine.

invasive pneumococcal disease, and
pHUS in particular, has been altered dramatically with the
introduction of pneumococcal vaccines. Most notably, rates of invasive pneumococcal disease have plummeted in children younger than 5 years, and non-vaccine serotypes have risen in prevalence [29]. The patient received PCV7 vaccination from her primary pediatrician, but did not receive subsequent PCV13 or PPVS23. Results of serotyping for this case are still pending, but the possibility that the infection was caused by a vaccine-preventable serotype underscores the importance of ensuring vaccine understanding among both community and specialist pediatricians.

This case highlights the diagnostic challenges that pHUS presents, and the importance of early recognition. Management often requires intensive supportive care with dialysis, transfusion with washed blood products and consideration of PLEX with 5% albumin. This case also highlights the need to consider pHUS in older patients with immunocompromising conditions such as nephrotic syndrome that increase the risk of invasive pneumococcal infection. Finally, proper vaccination practices are important to help prevent pneumococcal disease and its associated sequelae.

Conflict of interest statement
None declared.

References