Pneumococcal pneumonia with empyema and hemolytic uremic syndrome in children: report of three cases

Chih-Fang Lee1, Shu-Chih Liu2, Ko-Huang Lue1,3, Jung-Pin Chen4, Ji-Nan Sheu3,4

Divisions of 1Pediatric Immunology and 2Pediatric Infectious Diseases, Department of Pediatrics, Chung Shan Medical University Hospital, Taichung; 3Institute of Medicine, Chung Shan Medical University, Taichung; and 4Divisions of Pediatric Nephrology, Department of Pediatrics, Chung Shan Medical University Hospital, Taichung, Taiwan

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Streptococcus pneumoniae is an uncommon etiological organism in children with hemolytic uremic syndrome (HUS). Patients with S. pneumoniae-associated HUS commonly have a pneumonia or meningitis. Historically, S. pneumoniae-associated HUS usually has a poor clinical outcome. We report 3 pediatric cases of pneumococcal pneumonia-induced HUS. All 3 patients were <2 years old, had an empyema complicating pneumococcal pneumonia, and developed renal failure with oliguria and required peritoneal dialysis for a period of 9 to 26 days. All children received several transfusions of unwashed packed red cells and platelets. All of the patients survived. Of the 3 cases, 2 had a normal renal function at discharge, and 1 had a mild renal impairment at 16-month follow-up. Our report suggests S. pneumoniae-associated HUS remains a rare but severe complication of invasive pneumococcal infection in children. It is important for pediatricians to note that children with pneumococcal pneumonia with severe hematologic and renal dysfunction should be investigated for evidence of S. pneumoniae-associated HUS.

Key words: Empyema, hemolytic-uremic syndrome, pneumonia, renal function tests, Streptococcus pneumoniae

Hemolytic uremic syndrome (HUS), one of the common causes of acute renal failure in children, is characterized by the triad of microangiopathic hemolytic anemia, thrombocytopenia and acute renal failure [1,2]. The majority of HUS cases occur with a prodrome of infectious diarrhea following invasion of toxin-producing organisms including Escherichia coli and Shigella dysenteriae. The diarrhea-associated HUS is usually termed as a typical HUS [3]. The outcomes of diarrhea-associated HUS generally are good. Survival is >95% and long-term morbidity is <30% of patients [3]. HUS has been reported in the absence of infectious diarrhea and in association with other infections. Streptococcus pneumoniae is an uncommon etiological pathogen for inducing HUS, and S. pneumoniae-associated HUS is also termed as atypical HUS [4,5].

Historically, S. pneumoniae-associated HUS is characterized by high rates of mortality and morbidity [6]. S. pneumoniae produces the neuraminidase enzyme which removes N-acetylneuraminic acid from the cell membrane surface of erythrocytes, platelets and glomeruli to expose the Thomsen-Friedenreich antigen (T-antigen) [7-9]. The presence of naturally occurring anti-T immunoglobulin M (IgM) antibodies against the T-antigen accelerates agglutination and hemolysis of erythrocytes, platelet agglutination and glomerular capillary damage. Pneumococcal infection and T-antigen activation have been strongly associated with the characteristic features of HUS.

To our knowledge, 74 cases of S. pneumoniae-associated HUS have been previously reported in the English literature [4,5,9-27]. These patients commonly had a presentation of pneumococcal pneumonia or meningitis. We report 3 children who all had an empyema complicating pneumococcal pneumonia and the development of HUS. They underwent a period of...
peritoneal dialysis and all survived, 1 patient developing mild renal insufficiency.

Case Report

Case 1
A 21-month-old female patient presented with a 5-day history of fever, coryza and cough, but no diarrhea. She developed respiratory distress on the day of admission. On physical examination, body temperature was 39.2°C, pulse rate 154/min, respiratory rate 48/min, and blood pressure 138/88 mm Hg. On the day of admission, a blood smear disclosed marked red blood cell (RBC) fragmentation with anisocytosis, schistocytes and burr cells. Urinalysis showed proteinuria (3+) and occult blood (3+). Microscopic examination revealed numerous RBC with 15-18 white blood cells (WBC) per high-power field (HPF). The initial laboratory data are summarized in Table 1. The pleural fluid analysis revealed an exudate with a pH of 6.5, a protein level of 4.6 g/dL, a glucose level of 3 mg/dL, a lactate dehydrogenase (LDH) level of 58,550 IU/L, and a WBC of 45,200/mm³. Pleural fluid culture subsequently grew *S. pneumoniae*. The minimal inhibitory concentration (MIC) of penicillin of the isolate was 0.06 μg/mL. The *S. pneumoniae* isolate was susceptible to both penicillin G and cefotaxime. On the 4th hospital day, the patient became oliguric and edematous. Blood urea nitrogen (BUN) increased to 103 mg/dL and creatinine to 4.5 mg/dL. Transfusions of unwashed packed red cells (2 occasions) and platelets (2 occasions) were administered during the treatment course. The patient was treated with intravenous penicillin G and cefotaxime for 2 weeks. Serum BUN dropped to 25 mg/dL and creatinine to 0.8 mg/dL after 14 days of peritoneal dialysis. The patient had a normal urinalysis and renal function at 2-year follow-up.

Case 2
A 10-month-old female infant presented with a 5-day history of fever and productive cough. She developed respiratory distress and jaundice and was referred to our hospital. On physical examination, her vital signs were blood pressure 136/78 mm Hg, temperature 38.4°C.

Table 1. Clinical characteristics and initial laboratory data from patients with *Streptococcus pneumoniae*-associated hemolytic uremic syndrome

<table>
<thead>
<tr>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (months)</td>
<td>21</td>
<td>10</td>
</tr>
<tr>
<td>Gender</td>
<td>Female</td>
<td>Female</td>
</tr>
<tr>
<td>Disease (involved side)</td>
<td>Pneumonia with empyema (left)</td>
<td>Pneumonia with empyema (right)</td>
</tr>
<tr>
<td>WBC count (/mm³)</td>
<td>27,660</td>
<td>32,900</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>6.8</td>
<td>7.0</td>
</tr>
<tr>
<td>Platelet (/mm³)</td>
<td>12,000</td>
<td>17,000</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>23.8</td>
<td>30.8</td>
</tr>
<tr>
<td>BUN (mg/dL)</td>
<td>35</td>
<td>50</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>1.2</td>
<td>1.1</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>2.3</td>
<td>2.3</td>
</tr>
<tr>
<td>Total/direct bilirubin (mg/dL)</td>
<td>0.9/0.3</td>
<td>20.7/14.0</td>
</tr>
<tr>
<td>AST/ALT (IU/L)</td>
<td>87/24</td>
<td>270/42</td>
</tr>
<tr>
<td>LDH (IU/L)</td>
<td>4860</td>
<td>12,290</td>
</tr>
<tr>
<td>PT/PTT (seconds)</td>
<td>13.1/31.4</td>
<td>13.8/32</td>
</tr>
<tr>
<td>Fibrinogen (mg/dL)</td>
<td>358</td>
<td>426</td>
</tr>
<tr>
<td>Direct and indirect Coombs’ tests</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Duration of PD (days)</td>
<td>14</td>
<td>26</td>
</tr>
<tr>
<td>Hospital stay (days)</td>
<td>31</td>
<td>44</td>
</tr>
<tr>
<td>Estimated GFR (mL/min/1.73 m²) at discharge*</td>
<td>94.6</td>
<td>54.8</td>
</tr>
<tr>
<td>Outcome</td>
<td>RF recovery</td>
<td>Mild RF impairment at 16-month follow-up</td>
</tr>
</tbody>
</table>

Abbreviations: WBC = white blood cell; CRP = C-reactive protein; BUN = blood urea nitrogen; AST = aspartate aminotransferase; ALT = alanine aminotransferase; LDH = lactate dehydrogenase; PT = prothrombin time; PTT = partial thromboplastin time; PD = peritoneal dialysis; GFR = glomerular filtration rate; RF = renal function

*As described by Schwartz et al [28].
heart rate 132/min, respiratory rate 42/min. On the day of admission, a blood smear showed marked RBC fragmentation with schistocytes and helmet cells. The initial laboratory data are summarized in Table 1. Urinalysis showed occult blood (3+), marked proteinuria (3+), RBC 94-100/HPF and WBC 6-11/HPF. Pleural fluid analysis revealed an exudate with a pH of 7.0, a protein level of 3.4 g/dL, a glucose level of 7 mg/dL, a LDH level of 22,032 IU/L, and a WBC of 15,500/mm². Culture of the pleural fluid was subsequently positive for S. pneumoniae. The MIC of penicillin for the isolate was >4 µg/mL; the isolate was resistant to penicillin and susceptible to vancomycin. Two days after admission, the patient developed oliguria and generalized edema with a BUN of 145 mg/dL and creatinine of 2.8 mg/dL. Serum BUN decreased to 30 mg/dL and creatinine to 1.1 mg/dL after 26 days of peritoneal dialysis. Transfusions of unwashed packed RBC (3 occasions) and platelets (1 occasion) were given during the treatment course. The patient was treated with intravenous vancomycin for a total of 2 weeks. The patient was discharged with normal hepatic function and mild impaired renal function after 44 days of hospitalization. Renal function (BUN/creatinine, 31/0.6 mg/dL) was mildly impaired at 16-month follow-up.

Case 3

A 16-month-old boy was referred to our hospital because of persistent fever and productive cough for 1 week. On the day of admission, he developed respiratory distress and generalized edema. On physical examination, his vital signs were blood pressure 130/90 mm Hg, temperature 38.5°C, pulse 156/min, and respiratory rate 44/min. A blood smear showed marked RBC fragmentation with anisocytosis, schistocytes and helmet cells. Initial laboratory data are summarized in Table 1. Urinalysis results was 3+ for occult blood and 3+ for proteinuria; the sediment contained RBC >100/HPF and WBC 5-6/HPF. The pleural fluid analysis revealed an exudate with a pH of 7.0, a protein level of 3.1 g/dL, a glucose level of 37 mg/dL, an LDH level of 12,315 IU/L, and a WBC of 2500/mm². S. pneumoniae was subsequently isolated from the pleural fluid culture. The MIC of penicillin for the isolate was >4 µg/mL; the isolate was resistant to penicillin and susceptible to vancomycin. He developed anuria on day 3 with BUN 80.9 mg/dL and creatinine 4.1 mg/dL. Serum BUN decreased to 35 mg/dL and creatinine to 0.9 mg/dL after 9 days of peritoneal dialysis. He was treated with a 14-day course of vancomycin. Transfusions of unwashed packed RBC (1 occasion) and platelets (3 occasions) were administered during the treatment course. The patient was discharged from hospital with normal renal function after 27 days. He had a normal urinalysis and renal function at 4-month follow-up.

Discussion

All S. pneumoniae can produce neuraminidase, and are able to expose the T-antigen [29]. Patients with S. pneumoniae-associated disease have detectable serum neuraminidase activity, while patients with pneumococcal disease without HUS do not have detectable activity [7]. Detection of red cell T-antigen activation was not performed in any of the 3 patients because the diagnostic tests were not available in our hospital. However, all of the patients had an isolation of S. pneumoniae from pleural effusion culture, association between microangiopathic hemolytic anemia, thrombocytopenia, acute renal failure, and bacteriological evidence of pneumococcal infection. These findings were sufficient for the diagnosis of S. pneumoniae-associated HUS in these 3 patients.

The incidence of invasive pneumococcal infection is highest among children less than 2 years old [30]. Almost all children with S. pneumoniae-associated HUS were <2 years old in the previous reports [4,5,9-27]. All cases in this report were also <2 years old (from 10 to 21 months). T-antigen activation occurs more frequently in infants and small children [8]. This suggests that age-related antigen-antibody reaction may contribute to the tendency for the development of S. pneumoniae-associated HUS in very young children.

Treatment for S. pneumoniae-associated HUS is aimed at supportive care and treatment of the underlying infection. Transfusions with plasma-containing products can theoretically worsen the manifestations of HUS or exhibit life-threatening complications [4,12,13,26]. Traditional advice is to avoid the use of plasma products that contain naturally occurring anti-T antigen IgM in HUS patients. However, the necessity of routinely avoiding transfusions of plasma-containing blood products in S. pneumoniae-associated HUS patients is controversial in the literature. Recently, some investigators have questioned the risk of transfusing plasma in S. pneumoniae-associated HUS patients whose RBC are T-antigen activated, because the need for the important hemostatic components provided in plasma often outweighs the poorly substantiated risk of hemolysis associated with the passive infusion of...
anti-T-antigen [31-34]. Our cases received transfusions of unwashed packed RBC from 1 to 3 occasions and platelets from 1 to 3 occasions in the course, respectively. Massive hemolysis or disease worsening were not observed after transfusions of unwashed blood products in these patients. All of our patients survived. These outcomes are better than in the earlier studies and similar to the recent reports [4,5,26,27]. Our experience might support questioning of the traditional advice that routine transfusions of plasma-containing products should be avoided in patients with Streptococcus pneumoniae-associated HUS.

Acute mortality remains high in Streptococcus pneumoniae-associated HUS cases. Of 74 patients in the literature, 14 died (18.9%). Most of these patients died during the early phase of the disease from severe infections and neurological complications. We have no deaths in our patients. Mortality from this condition appears to have been reducing in recent years [4,5,26,27]. Of 30 cases in the most recent 4 studies [4,5,26,27], only 1 death (3.3%) was found; this is similar to the mortality of diarrhea-associated HUS. It is suggested that the decreased mortality rates can be attributed to early recognition of the disease, advances in the intensive care of critically ill patients, dialysis intervention and judicious use of blood products rather than the alterations of bacterial virulence and disease severity. Generally, Streptococcus pneumoniae-associated HUS patients are more likely to require dialysis (range, 75% to 100%) and had a longer hospital stay than other patients with HUS. All of our patients required peritoneal dialysis for a period of 9 to 26 days and had a hospital stay of 27 to 44 days. It is similar to previous reports.

In summary, Streptococcus pneumoniae-associated HUS remains a rare but severe complication of invasive pneumococcal infection in children. Our report suggests that early recognition of the disease, intensive care and early dialysis intervention of the patients may increase the survival rate and may prevent the development of renal dysfunction.

References
S. pneumoniae and hemolytic uremic syndrome


