Case 22. A 2-Year-Old Girl with Community-Acquired Pneumonia Followed by Thrombocytopenia and Anemia: *Streptococcus pneumoniae* Associated with Hemolytic Uremic Syndrome

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Keywords

Community-acquired pneumonia · *Streptococcus pneumoniae* · Hemolytic uremic syndrome · Thomsen-Friedenreich antigen

Key Points

- Hemolytic uremic syndrome is a complication in 0.4–0.6% of IPD cases, which is characterized by microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury.
- The symptoms of HUS typically developed 3–13 days (most at 7–9 days) after the onset of the symptoms related to pneumococcal infection.
- In the circumstance of HUS, the fibrinogen level, prothrombin time, and partial thromboplastin times are usually normal or slightly elevated and active bleeding is rare.
- Blood transfusion with washed blood product and avoiding the plasma transfusion remains an important concept because these procedures are thought to reduce the exposure to T antigen.
- Renal placement therapy is indicated for anuria and deteriorated renal function.

Case Report

A previously healthy 2-year-9-month-old girl was admitted after 5 days of fever, productive cough, and rhinorrhea. A chest radiograph revealed segmental consolidation in right lower lobe of lung, consolidation with air-bronchogram over left lower lobe of lung (Fig. 1). Hemogram disclosed leukocyte count 5000/μL (normal range: 6000–10,400), with elevated band form of 27%, hemoglobin 11.0 g/dL (normal range: 11.6–13.7), platelet count 100,000/μL (normal range: 150–400), and elevated C-reactive protein (CRP): 322.57 mg/L (normal range: <5 mg/L) on

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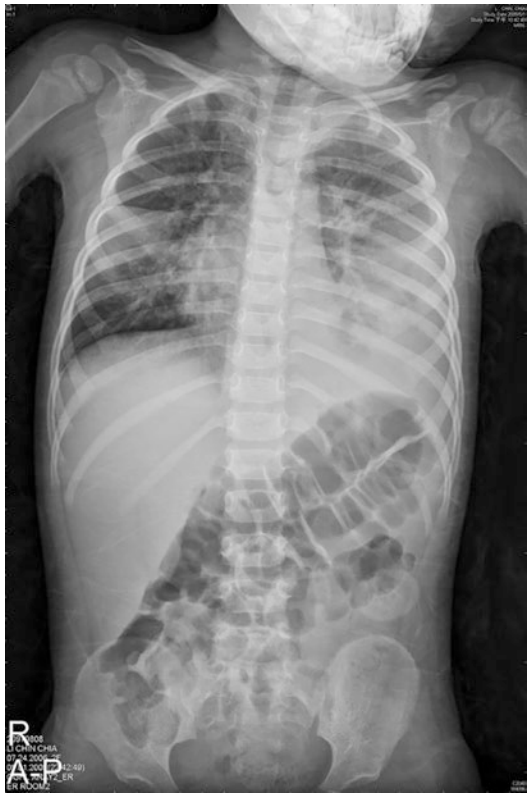

Fig. 1 On the day of admission, the chest plain film disclosed consolidation with air-bronchogram over left lower lobe and segmental consolidation in right lower lobe

admission. Urine pneumococcal antigen test (Binax NOW) showed a positive result. Empiric ceftriaxone (75 mg/kg/day) and azithromycin (10 mg/kg/day) were prescribed for severe community-acquired pneumonia. The patient was then transferred to pediatric intensive care unit (PICU) on the day of admission because of increased respiratory distress and oliguria. She was intubated for ventilator support. Leukopenia (3800/μL) with bandemia (band form 34%), anemia (hemoglobin: 10.5 g/dL) and thrombocytopenia (platelet count: 37,000/μL) was found on hospital day 2. Antibiotics were adjusted to vancomycin (~60 mg/kg/day) and ceftriaxone (100 mg/kg/day). A chest ultrasound examination reported lobar pneumonia in right middle lobe and left lower lobe with suspicious necrotic change over left lower lobe. Bilateral parapneumonic effusion was visualized. A pleural effusion specimen from left side after a chest tube insertion showed cloudy, leukocyte count 3760/μL with 97% neutrophils and 3% lymphocytes, red blood cell 3120 per microliter, and gram stain disclosed gram positive cocci +++. Both blood culture and pleural effusion culture subsequently yielded *Streptococcus pneumoniae,* serotype 14. On hospital day 3, there was progressive anemia (hemoglobin: 7.7 g/dL) and thrombocytopenia (7000/μL). Coagulation profiles showed prothrombin time 15.9 s (normal range: 10.0–13.0), partial thromboplastin time 48.4 s (normal range: 24.0–31.0), and fibrinogen level 687 mg/dL (normal range: 190–380). Peripheral blood smear disclosed fragmented red blood cells and Burr cells. Oliguria with daily urine output 0.25 mL/kg/h and elevated serum creatinine level (1.57 mg/dL) were also noted. The Thomsen-Friedenreich antigen was positive. Pneumococcal pneumonia with hemolytic uremic syndrome (HUS) was impressed. Blood was seen in the endotracheal tube, and thus washed red blood cell and leukocyte-poor platelet were transfused. Anuria then developed and continuous renal replacement therapy (CRRT) was applied. Anuria improved and the CRRT was discontinued on day 7. Anemia and thrombocytopenia also improved. Fever continued during hospitalization. Non-enhanced computed tomography of chest was performed on hospital day 8 and disclosed lobar pneumonia over left lower lobe and empyema (Fig. 2). The chest tube was removed on day 13 and the endotracheal tube was extubated on day 14. A pneumatocele was found on the chest plain film on day 15, further chest computed tomography revealed necrotizing pneumonia over left lower lobe and hydropneumothorax, suggestive of bronchopleural fistula. An operation of decortication and lobectomy of left lower lobe by video-assisted thoracoscope was performed by the pediatric surgeon. Meropenem was ever substituted for ceftriaxone between day 8 to day 18 and vancomycin was discontinued on day 12. After fever subsided on day 18, ceftriaxone was substituted for Meropenem and then shifted to oral form of amoxicillin (100 mg/kg/day) on day 23–29. The pathology report disclosed necrosis and abscess, suggesting acute necrotizing pneumonia. A follow-up CXR film showed significant improvement (Fig. 3). She was discharged on day 27.

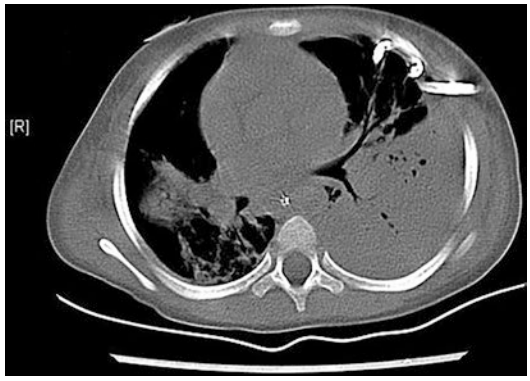

Fig. 2 Chest computed tomography without contrast (concerning acute renal failure) on day 8 of admission reports consolidation with air-bronchogram in left lower lobe, left site empyema status post pigtail catheter drainage and segmental consolidation in right upper lobe and right lower lobe

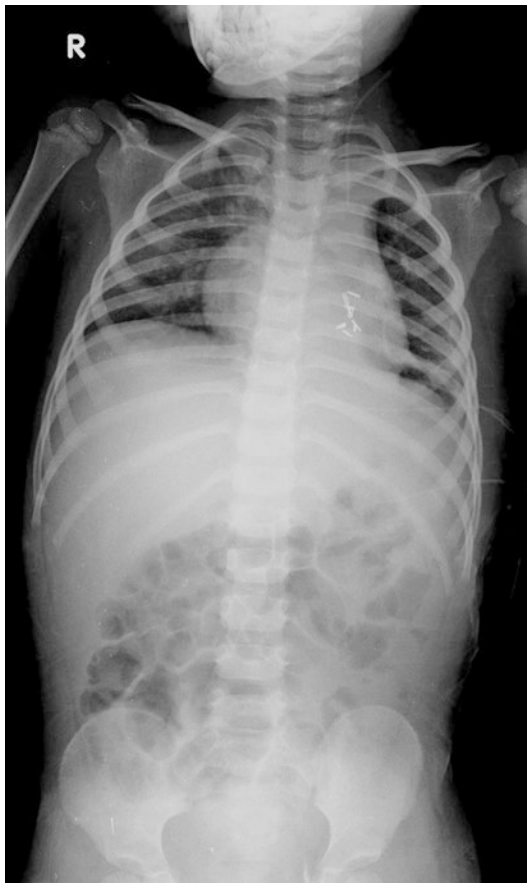

Fig. 3 Before discharge (admission day 21), chest plain film disclosed minimal consolidation over left lower lobe and post-operative metallic clips

Discussion

Streptococcus pneumoniae (*S. pneumoniae*) is a gram-positive, facultative anaerobic bacteria. There are over 90 known serotypes for different capsular expression. *S. pneumoniae* can colonize at respiratory tract at all ages among humans, and children bear higher colonization rate than adults. *S. pneumoniae* can cause diseases as well. Manifestations of pneumococcus infection range from upper and lower respiratory tract infection, sepsis, bacteremia to meningitis. The confirmatory diagnosis of invasive pneumococcal disease (IPD) is defined as isolation of *S. pneumoniae* from a normally sterile site of body. IPD causes morbidity and mortality in clinical practice. After introducing the pneumococcal conjugate vaccine (PCV), the rate of IPD has decreased. In the children, the major serotypes causing IPD were serotype 14, 19F, and 6B before the vaccine era, while these serotypes declined in the post-vaccine era. In Taiwan, IPD was most frequently seen in patients aged between 2 and 5 years. Taiwan introduced PCV7 in 2006 and PCV10 in 2010 used in the private sector in children aged under 5 years. However, IPD caused by serotype 19A gradually increased. Therefore, Taiwan Centers for Disease Control started to introduce PCV13 in children age 2–5 years first and then shifted to national immunization program during infancy. The incidence of IPD decreased thereafter. IPD caused by serotype 19A declined as well. Instead, serogroup 15 became the leading serotypes of IPD in pediatric group aged under 5 years.

Hemolytic uremic syndrome (HUS) is a complication in 0.4–0.6% of IPD cases, which is characterized by microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury. Traditionally, most of the HUS cases are caused by Shiga-like toxin producing *Escherichia coli* (STEC); however, *S. pneumoniae* infection, complement pathway dysregulation, and inborn errors of metabolism also contribute to the occurrence of HUS. In the non-STEC HUS cases, pneumococcal infection-associated HUS accounted for 40%. The pathophysiology of HUS is now believed to be associated with TF antigen activation. The Thomsen-Friedenreich antigen

(T antigen) is a structure on the surface of erythrocytes, platelets, and glomerular endothelial cells. The T antigen is normally shielded by neuraminic acid. Pneumococcus produce neuraminidase which is capable of exposing the normally hidden T antigen by cleaving the N-acetylneuraminic acid. The unmasked T antigen subsequently bound to the anti-T IgM antibodies and resulted in the HUS. In addition, the role of the alternate pathway of complement's contribution to the HUS is under investigation. *S. pneumoniae* associated HUS (P-HUS) was first reported in the 1970s. Empyema and meningitis are mostly seen in P-HUS. Decades after the first case had been reported, high mortality rate to 50% and the development of chronic kidney disease or hypertension in two-third of the survivors were reported. The prognosis dramatically improved in the following years, possibly related to the advanced technique in critical care skill. All serotypes of *S. pneumoniae* have the neuraminidase, but the activity varied. Thus, theoretically, different activities and likelihood also differ among serotypes. In the pre-vaccine era, it is not surprising that serotype 14 was the most associated serotype; other attributable serotypes were 6B, 9 V, 19, 3, 8, 7, and 23F. In the post 7-valent pneumococcal conjugate vaccine era, 19A became the most frequently seen serotype. Clinically, the symptoms of HUS typically developed 3–13 days (most at 7–9 days) after the onset of the symptoms related to pneumococcal infection. The accurate diagnosis of P-HUS is still under debate. In most cases, the diagnosis is made in the combination of clinical and laboratory features and evidence of pneumococcal infection. According to the Canadian Pediatric Society, the P-HUS is defined in two categories. Definite cases are those with a thrombotic microangiopathy on renal pathology, in addition to clinical features of HUS and evidence of pneumococcal infection. Some experts considered the positive Coombs test instead of the pathology report is enough for diagnosis. Possible cases are those difficult to distinguish between severe infection-related end organ failure or HUS. The European Pediatric Study Group for HUS recommended the diagnosis of P-HUS made by a HUS combined with a proven or suspected invasive pneumococcal infection. The detection of T-antigen also plays a role in the diagnosis by many experts, using the direct Coombs test, polyagglutination test, and peanut lectin agglutination test. The detection of P-HUS is a dilemma to differentiate HUS from disseminated intravascular coagulation (DIC). Both of these conditions may occur in severe infection and presented with anemia, thrombocytopenia, and renal failure. However, in the circumstance of HUS, the fibrinogen level, prothrombin time, and partial thromboplastin times are usually normal or slightly elevated and active bleeding is rare.

The management goal for P-HUS is supportive care. Adequate fluid supplement, maintaining the electrolytes balance, nutrition support, and appropriate antibiotics prescription are the gold standard. The American Academy of Pediatrics suggests non-critically ill and previously healthy children with nonmeningeal invasive pneumococcal disease be treated with penicillin or ampicillin empirically. In critically ill patients, Vancomycin plus a third generation of cephalosporin were suggested. Blood transfusion with washed blood product and avoiding the plasma transfusion remains an important concept because these procedures are thought to reduce the exposure to T antigen. In some circumstances, renal placement therapy is indicated for anuria and deteriorated renal function.

Further Reading

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