Haemolytic Uraemic Syndrome Associated with Pneumococcal Sepsis

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Abstract

Haemolytic uraemic syndrome is an unusual and serious complication of pneumococcal sepsis. We reported a boy presenting with pneumococcal sepsis who subsequently developed haemolytic anaemia, thrombocytopenia and acute renal failure. Washed red cell products, platelet concentrates and renal replacement therapy had been instituted in this patient. The boy recovered well and needed periodic evaluation of long term renal outcome.

Key words

Acute renal failure; Haemolytic uraemic syndrome; Pneumococcal septicemia

Case Report

A previously healthy 19-month-old Chinese boy presented with fever and cough for three days and was admitted because of persistent fever, cough and dyspnoea. On admission he got a temperature of 39°C and mild respiratory distress. Physical examination revealed respiratory rate of 50 breaths/min., decreased air entry on left side of chest with coarse crepitations, and SaO2 of 94%. The chest radiograph showed left lower lobe consolidation. The boy was given intravenous fluid and parenteral augmentin after sepsis workup. Initial laboratory results were as follows: Hb 12 g/dl, WBC 12.0 x 10^9/l, platelet 205 x 10^9/l, normal serum electrolytes and blood urea. Blood culture grew Gram-positive cocci.

In the next few hours, his respiratory status worsened with grunting and increasing tachypnoea. The child looked pale and lethargic, and little urine output was observed. He needed nasal oxygen of 1 l/min. Repeated chest radiograph showed complete opacification of left lung. The laboratory tests revealed Hb dropped to 8.8 g/dl, platelet 15 x 10^9/l, normal serum electrolytes and blood urea. Blood culture grew Gram-positive cocci.

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He was transferred to paediatric intensive care unit (PICU) for mechanical ventilation and dopamine infusion. Augmentin was replaced with vancomycin and cefotaxime. He developed progressive azotemia, thrombocytopenia and metabolic acidosis. He remained oliguric and was treated with fluid restriction and diuretics. Echocardiogram showed no vegetation or pericardial effusion, and renal ultrasound did not detect any renal vein thrombosis. Bronchoscopy yielded small amount of bronchial aspirates, which showed no positive growth. On the second day of PICU care, the patient developed anuria with blood urea rising from 20 to 35 mmol/l, creatinine 162 to 261 µmol/l. Continuous hemofiltration was instituted. Dopamine was stopped because of hypertension. Hydralazin had been given for two days. Vancomycin dosage was adjusted titrating against the drug trough level because of impaired renal function. Washed blood products including red cells and platelet concentrate were given repeatedly in the next few days for persistent haemolysis and thrombocytopenia. Total parenteral nutrition was started on day 3.

Chest radiograph on day 3 showed left lower lobe consolidation accompanied by pleural effusion. Ten millilitres of blood stained fluid obtained by pleural tapping, but culture did not reveal any positive growth.
Ventilatory support was reduced after improvement in respiratory condition on day 5. He was extubated on day 7 and continued to be on renal replacement therapy. On day 12 of PICU care, CT thorax demonstrated a large fluid collection in the posterolateral region of the left lung suggestive of empyema. A chest drain was inserted and a significant amount of serosanguinous fluid was yielded. Meropenem was added. There was ongoing haemolysis requiring multiple transfusions.

Haemolysis became less severe with stable haemoglobin level on day 15. The urine output improved on day 16 (>1 ml/kg/hour) and the renal replacement therapy was discontinued on day 19. Chest drain was taken off after five days of placement, and repeated CT thorax showed a small left sided pleural fluid remaining. The child was clinically stable and the pleural effusion was treated conservatively.

By day 24 he was discharged from PICU. The renal function and blood pressure were normal. The haemoglobin was 9.3 g/dl, and platelet count was 198x10^9/l. Vancomycin was given for two weeks and meropenem for four weeks. He was well and discharged on day 41. The boy has been regularly seen in out-patient clinic with normal blood pressure, urinalysis and renal function at 18 months follow-up.

Discussion

Haemolytic uraemic syndrome (HUS) is usually associated with enterohaemorrhagic Escherichia coli serotype O157:H7 infection, and is a major cause of acute renal failure in children, accounting for approximately 90% of cases following a diarrhoeal prodrome. It is believed that verocytotoxin or Shiga-like toxins produced by bacteria induces cascade of inflammatory events for disease manifestation.

Streptococcus pneumoniae infections of the lung, rarely meninges, are the most commonly reported cases of nondiarrhoeal HUS in children. HUS is an unusual and serious manifestation of the invasive Streptococcus pneumoniae infection. The association between HUS and pneumococcal infection was first described by Fisher in 1971. The syndrome is characterized by microangiopathic haemolytic anaemia, thrombocytopenia and acute renal failure. Neuraminidase produced by pneumococci removes N-acetylneuraminic acid from cell membrane surface exposing the Thomsen-Friedenreich antigen (T-antigen) on erythrocytes, platelets, and glomerular capillary walls. The T-antigen reacts with anti-T antibody in most normal sera, resulting in haemolysis, thrombocytopenia, and thrombotic renal microangiopathy. It has been suggested that this is the pathogenesis of HUS due to Streptococcus pneumoniae infections.

HUS associated with pneumococcal infection usually affects children age <2 years, with illness requiring dialysis and longer hospital stay than HUS patients associated with Ecoli O157:H7. The patients with pneumococcal pneumonia or sepsis usually developed HUS during the acute phase of the illness. It has been found that Streptococcus pneumoniae causes a more severe form of the illness. Mortality for Ecoli O157:H7 associated HUS is approximately 5%, and 5% of survivors left with renal sequelae, but there is little published data concerning the morbidity and mortality of HUS associated with Streptococcus pneumoniae.

The mainstay treatment for diarrhoeal associated HUS is supportive and includes fluid restriction, maintenance of electrolyte balance, nutritional support, and control of hypertension and seizures. Packed red cell transfusions are administered for severe anaemia, and platelet transfusions are reserved for those with severe thrombocytopenia. Renal replacement therapy, either peritoneal dialysis or hemodialysis, is indicated for anuria, severe uncontrollable hyperkalaemia, and fluid overload with pulmonary oedema. Other treatments include plasmapheresis, use of methylprednisolone, transfusion of fresh frozen plasma, intravenous administration of immune globulin, but their efficacy has not been proven.

For patients with Streptococcus pneumoniae associated HUS, the treatment is similar to that of diarrhoecal associated HUS. However serum-containing blood products should be avoided based on the finding of the presence of T-antigen activation. Anti-T free blood products (like washed red cells and washed platelet concentrate) are recommended. More importantly, fresh frozen plasma is contraindicated. Washed red cell transfusion seems to have reduced rate of haemolysis. The positive direct Coombs test in our patient could be due to the presence of anti-T antibody on the red blood cells or anti-T IgM in the polyvalent Coombs antisera. Dialysis is often necessary, and early institution of renal replacement therapy can reduce mortality and morbidity of Streptococcus pneumoniae induced HUS. Renal biopsy revealed pronounced mesangial sclerosis and thickening of capillary loops, however there has been no study relating such pathology to the long-term renal outcome.

Use of vancomycin is recommended for invasive pneumococcal infections in critically ill patients, but we should maintain close surveillance on altered drug clearance resulting from acute renal failure. For pneumococci that are nonsusceptible to penicillin, cefotaxime and ceftriazone, combination therapy of vancomycin plus either of the above antibiotics can have synergistic effect and may prevent emergence of drug
Although empyema in children associated with pneumonia is uncommon, there has been an increase in reported cases in Cabrera and Hardie studies. The best predictor of chronic renal sequelae is the duration of anuria during the acute phase, virtually anuria longer than one week or oliguria exceeding two weeks were usually left with chronic renal disease in postdiarrhoeal HUS cases. However no data reported on the long term renal outcome in HUS associated with *Streptococcus pneumoniae*.

Our patient had the duration of anuria of six days, oliguria of 10 days, maintaining on dialysis for 18 days. Regular evaluation of renal function including urinalysis will be required for long-term renal outcome. He remained well at subsequent follow-up.

In summary we should maintain high level of vigilance for the possibility of development of HUS in patients with invasive pneumococcal disease, for early recognition with use of blood products free of T-antigen antibody and various supportive cares such as dialysis can improve the outcome for these children.

**References**