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SHORT REPORT

Streptococcus pneumoniae-associated haemolytic uremic syndrome following influenza A virus infection

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Abstract Influenza virus is a seasonal cause of community-acquired pneumonia, and *Streptococcus pneumoniae* is one of the most common pathogens causing secondary bacterial pneumonia. *S. pneumoniae*-induced haemolytic uremic syndrome is an uncommon condition mainly observed in young children. We present a patient who had invasive pneumococcal disease and haemolytic uremic syndrome. Simultaneous viral cultures grew influenza A. To the best of our knowledge, this is the first such reported case.

Keywords *Streptococcus pneumoniae* infection · Haemolytic uremic syndrome influenza A virus

Introduction

Streptococcus pneumoniae is a well-known causative pathogen of secondary bacterial pneumonia following influenza virus infection [3], and *S. pneumoniae*-induced haemolytic uremic syndrome (HUS) is an uncommon condition seen primarily in young children [10]. Synergetic effects between the influenza virus and bacteria have been suggested, and severe pneumonia frequently results in patients coinfected with influenza virus and bacteria [8]. Evidence exists that influenza virus alters the host in a way that predisposes to the adherence, invasion and induction of disease by *S. pneumoniae*. Alteration of the immune response either by reducing the ability of the host to clear *S. pneumoniae* or by amplification of the inflammatory cascade likely contributes to the severity of the disease [8].

HUS is one of the most common causes of acute renal failure in children [9]. Atypical HUS is characterised by a microangiopathic haemolytic anaemia, acute renal failure and thrombocytopenia in the absence of a diarrhoeal prodrome. An increasingly recognised cause of atypical HUS is invasive *S. pneumoniae* infection. Historically, *S. pneumoniae*-associated HUS has been characterised by high morbidity and mortality rates compared to *Escherichia coli* O157 gastroenteritis-associated HUS [1, 11]. Influenza A virus itself is also reported to be associated with HUS, but this is very rare and only five patients have been reported [12]. We describe a child who presented with *S. pneumoniae* pneumonia, sepsis and HUS, and influenza virus coinfection was proved later by viral culture and polymerase chain reaction (PCR).

Case report

A previously healthy 44-month-old girl, who had suffered from cough and fever for 7 days, was admitted to our hospital. She also had abdominal pain and oliguria. On admission, she had hypertension (blood pressure 120/58 mmHg). Laboratory examinations showed plasma sodium 133 mEq/l, potassium 4.6 mEq/l, blood urea nitrogen 75 mg/dl, creatinine 1.76 mg/dl, total bilirubin/direct bilirubin 12.6/6.1 mg/dl and lactate dehydrogenase 2,385 U/l. The haemoglobin concentration was 12.3 g/dl and fell to 8.6 g/dl within 10 h; the leukocyte count was 2,900/μl and the platelet count was 13,000/μl. A chest X-ray showed left lower lobe pneumonia (Fig. 1). Endotra-

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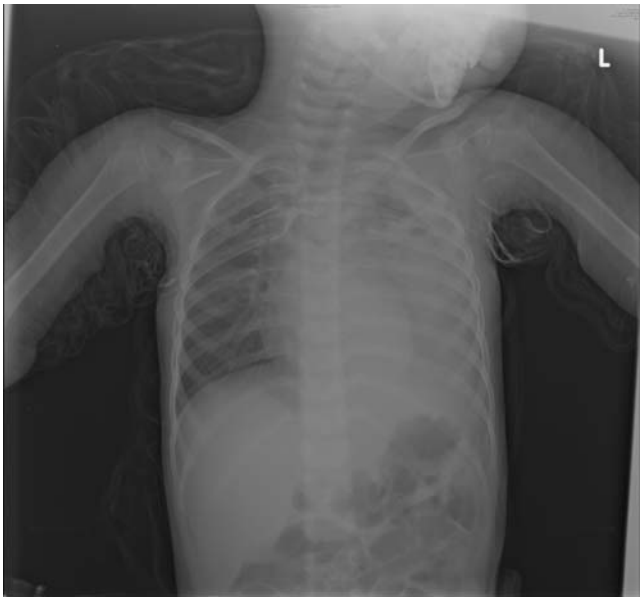

Fig. 1 Left lower lobe pneumonia is seen on the chest X-ray

cheal intubation with positive ventilation was performed because of hypoxia and respiratory failure.

During hospitalisation, the blood smear was positive for red blood cell fragments. She received frequent transfusions of leukocyte-poor platelets and washed red blood cell concentrate.

Vancomycin and meropenem were prescribed initially, but left-side pneumothorax developed on the ninth day of admission. Pigtail drainage was performed, and chest computed tomography revealed necrotising pneumonia, a parapneumonic effusion and bronchopleural fistula. For the necrotising pneumonia and bronchopleural fistula, decortication and partial resection of the left lower lobe were performed via video-assisted thoracoscopy on the 15th day of admission. Penicillin-susceptible *S. pneumoniae* was cultured from blood and sputum collected on the first day of admission. The urine pneumococcus antigen test was positive. The antibiotics were changed to high-dose penicillin G based on the results of culture sensitivity. Throat virus culture yielded influenza A, and influenza A PCR was also positive for H1 type. Erythrocyte Thomsen–Friedenreich cryptantigen activation was positive.

She required assisted ventilation for 17 days. In addition, continuous venovenous haemofiltration and peritoneal dialysis were performed on the second day of admission due to anuria, and dialysis was required for 33 days. On the 23rd day of admission, brain magnetic resonance imaging (MRI) was arranged for altered consciousness after extubation, which revealed diffuse cerebral and mild cerebellar atrophy. The girl was discharged home with oral amoxicillin treatment after 62 days of hospitalisation having normal renal function variables and mild proteinuria.

Discussion

Influenza A virus accounts for significant mortality and morbidity despite major efforts in prevention and treatment. The World Health Organization estimates that annual influenza epidemics cause three to five million severe illness and 250,000 to 500,000 deaths each year in the developed world alone [7]. Morbidity and mortality may result from the development of respiratory complications, including pneumonia [7]. An increase in bacterial pneumonia severity due to coinfection with influenza virus has been reported, and cases of fulminant primary influenza pneumonia that developed into secondary bacterial pneumonia have also been described [7, 10]. Based on the historical importance of pneumonia as a cause of death during pandemic influenza, the increasingly likely possibility that highly pathogenic avian influenza viruses and more recently novel influenza A (H1N1) virus will trigger the next worldwide pandemic underscores the interaction between influenza virus and bacterial pathogens such as *S. pneumoniae* [7]. Influenza virus alters the lungs in a way that predisposes to adherence, invasion and induction of disease by pneumococcus [7]. These synergetic effects might be enhanced by host factors mediated through immunologic reactions, including leukopaenia, neutropaenia and depressed neutrophil function, as well as by epithelial damage, changes in airway function and upregulation and exposure of epithelial activated receptors [8]. In addition to respiratory complications, influenza A can also cause disorders of the central nervous system, such as encephalitis and encephalopathy. In our patient, a transient consciousness disturbance was recognised with abnormal MRI findings. This condition may be explained by the influenza virus infection.

Haemolytic uremic syndrome caused by influenza A has been reported [12]. However, an increasingly recognised cause of atypical HUS is invasive *S. pneumoniae* infection. *S. pneumoniae*-associated HUS is an uncommon but severe condition observed mainly in young children [3]. The pathogenesis of *S. pneumoniae*-associated HUS is thought to result from exposure of the T antigen on the surface of erythrocytes and glomerular endothelial cell by neuraminidase secreted by S. *pneumoniae*. The T antigen reacts with serum IgM antibodies against it, causing haemolysis and damage to glomerular endothelial cells, resulting in HUS [2, 3]. Influenza virus also has a potential role in *S. pneumoniae*-associated HUS. The roles of neuraminidase in influenza virus-induced membrane fusion have been investigated, and influenza neuraminidase has been reported to participate in erythrocytes fusion and haemolysis. This may suggest the potential role of influenza neuraminidase as a potentiating factor in the pathogenesis of *S. pneumoniae*-associated HUS [6]. Another important mechanism under-

lying atypical HUS involves the complement system. Almost all patients with atypical HUS have a defect in alternative pathway, such as mutations in the genes for complement factor H, factor I and membrane cofactor protein [11].

Early recognition of HUS caused by *S. pneumoniae* infection is important because the use of plasma or plasma-containing blood products may aggravate the disorder due to the addition of donor IgM to the T antigen [4, 11]. Also, fluid overload should be avoided due to renal failure [5, 11]. Those patients recognised early in their course have an excellent prognosis for survival, whereas unrecognised ones have a high mortality [4]. Several reports have highlighted the high incidence of concurrent empyema in patients with *S. pneumoniae*-associated HUS, which could be explained by a heavy bacterial load. The presence of parapneumonic empyema may be a particular risk factor for HUS [1]. During the influenza season, secondary pneumococcal pneumonia after influenza should be recognised and treated early because the fatality rate remains high. Children with pneumococcal disease, especially with empyema and severe haematological or renal abnormalities, should be investigated for evidence of HUS. Effective vaccination and timely use of the neuraminidase inhibitor class of drugs will have an impact on the incidence and severity of secondary bacterial complications during a pandemic [7].

References

1. Brandt J, Wong C, Miham S, Roberts J et al (2002) Invasive pneumococcal disease and haemolytic uremic syndrome. Pediatrics 110:371–376
2. Cochran JB, Panzarino VM, Maes LY et al (2004) Pneumococcus-induced T-antigen activation in haemolytic uremic syndrome and anemia. Pediatr Nephrol 19:317–321
3. Copelovitch L, Kaplan BS (2008) *Streptococcus pneumoniae*-associated hemolytic uremic syndrome. Pediatr Nephrol 23:1951–1956
4. Erickson LC, Smith WS, Biswas AK et al (1994) *Streptococcus pneumoniae*-induced haemolytic uremic syndrome: a case for early diagnosis. Pediatr Nephrol 8:211–213
5. Gilbert RD, Argent AC (1998) *Streptococcus pneumoniae*-associated haemolytic uremic syndrome. Pediatr Infec Dis J 17:530–532
6. Huang RT, Dietsch E, Rott R (1985) Further studies on the role of neuraminidase and the mechanism of low pH dependence in influenza virus-induced membrane fusion. J Gen Virol 66(Pt 2):295–301
7. McCullers JA (2006) Insights between influenza virus and pneumococcus. Clin Microbiol Rev 19:571–582
8. McCullers JA (2004) Effect of antiviral treatment on the outcome of secondary bacterial pneumonia after influenza. J Infect Dis 190:519–526
9. Moghal NE, Brocklebank JT, Meadow SR (1998) A review of acute renal failure in children: incidence, etiology and outcome. Clin Nephrol 49:91–95
10. Mohan SS, Vinay N, Cunha BA (2005) Post-viral influenza *Streptococcus pneumoniae* pneumonia in an intravenous drug abuser. Heart Lung 34:222–226
11. Scheiring J, Rosales A, Zimmerhackl LB (2009) Clinical practice: Today's understanding of the haemolytic uraemic syndrome. Eur J Pediatr Aug 26. [Epub ahead of print]
12. Watanabe T (2001) Hemolytic uremic syndrome associated with influenza A virus infection. Nephron 89:359–360