STREPTOCOCCAL PNEUMONIA ASSOCIATED HAEMOLYTIC URAEMIC SYNDROME (SP-HUS) IN A 4-YEAR-OLD BOY - A RARE BUT SERIOUS CONDITION. WHAT SHOULD PRIMARY CARE PHYSICIANS KNOW?

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ABSTRACT

We report a case of streptococcal pneumonia associated haemolytic uraemic syndrome (SP-HUS) in a 4-year old child. It is a rare complication of invasive streptococcus pneumoniae infection. This article touches on the how the patient's mother was unusually calm after hearing the bad news. Factors that could account for her reaction are explored. Other issues triggered by this case were questions on the pathophysiology, clinical features, treatment and prognosis of this complication. We also discussed "catch-up" vaccination for children immunised with the old 7-valent pneumococcal vaccine, early diagnosis of community acquired pneumonia, recognising antibiotic failure and SP-HUS.

Keywords:
Streptococcus pneumonia, Haemolytic uraemic syndrome, Acute renal failure, Anaemia, Thrombocytopenia, Complication

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INTRODUCTION

This 4-year-old child presented when I was doing my paediatric rotation as a first year Family Medicine Resident towards the end of 2011. Streptococcal pneumonia associated haemolytic uraemic syndrome (SP-HUS) is a rare but serious complication of pneumococcal infection. Primary care physicians need to have a high index of suspicion in a paediatric patient with community acquired pneumonia that is not resolving.

PATIENT'S REVELATION: WHAT HAPPENED?

A 4-year-old Chinese boy first presented to a tertiary hospital's children's emergency with a 4-day fever of temperature 39°C, cough and rhinorrhea. His parents were also recently ill with upper respiratory tract symptoms. There was no travel history. His vaccinations were up to date, and he had received a single dose of the 7-valent pneumococcal protein conjugate vaccine 2 years earlier. This boy has a history of H1N1 influenza virus-induced febrile status epilepticus 2 years earlier and is on sodium valproate. He has been asymptomatic since and is neuro-developmentally appropriate for his age.

On clinical examination, he was non-toxic and not in respiratory distress. Temperature was 39.1°C, heart rate 135/min, respiratory rate 20/min and spO2 100% on room air. He had crepitations in both lungs. A full blood count showed a white cell count of 5.14 x 10^9/L. Chest X-ray (Figure 1) showed bilateral hilar infiltrates. He was diagnosed with atypical pneumonia and sent home with oral clarithromycin. Two days later, he re-presented to the emergency department again with persistent fever and body aches. Temperature was 38.7°C and vital signs were comparable to his previous visit. His parents were advised to continue clarithromycin. He returned three days later with worsening cough and body aches. He was lethargic and dehydrated. There were bilateral crepitations, decreased breath sounds, and dullness to percussion over the right lung base. Repeat chest X-ray (Figure 2) showed bilateral infiltrates with a right pleural effusion. Laboratory investigations showed leukopenia (TW3.81 x 10^9/L) and CRP of 515 mg/L. Haemoglobin, urea and creatinine levels were normal.

He was admitted. Blood cultures were sent off. Intravenous ceftriaxone was started. An ultrasound thorax showed a right-sided loculated pleural effusion with thin internal septations and fibrous material. There was consolidation of the whole right lower lobe.

On day 11 of illness, he had persistent lower abdominal discomfort with episodes of watery stool. He was anuric for 10 hours, and was tachycardic (180beats/min) and tachypneic (64 breaths/minute). Generalised oedema, a gallop rhythm, hepatomegaly and ascites were present.

FIGURE 1. CHEST X-RAY OF PATIENT ON DAY 4 OF ILLNESS

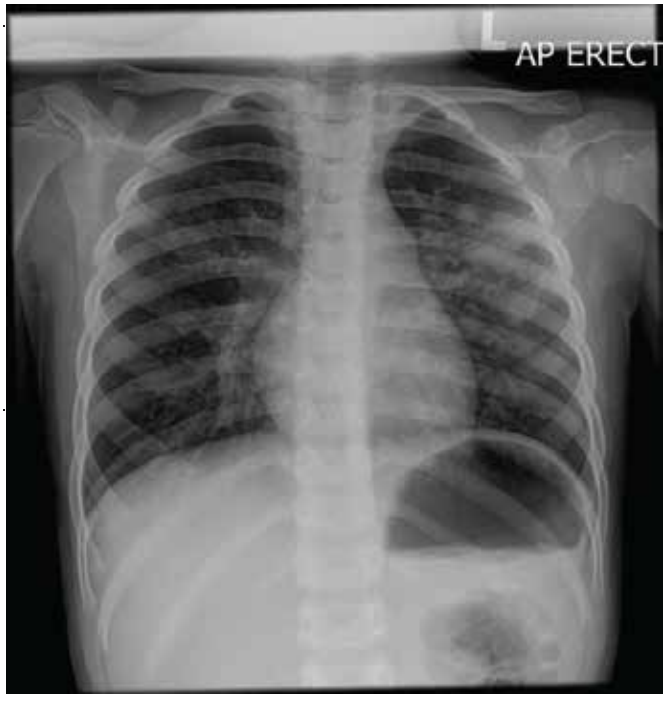

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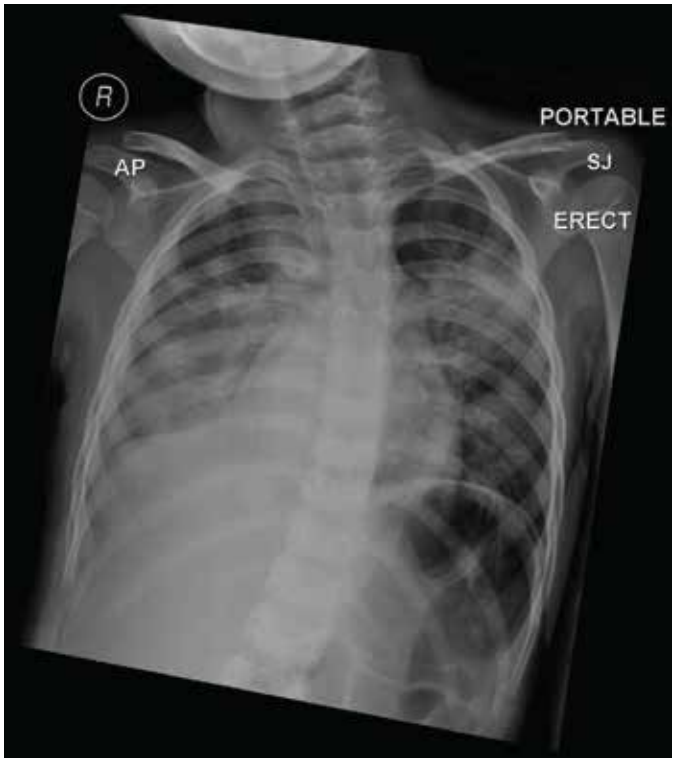
FIGURE 2. CHEST X-RAY OF PATIENT ON DAY 9 OF ILLNESS



He was transferred to the paediatrics intensive care unit (PICU) for monitoring and ventilatory support. Investigations supported a diagnosis of SP-HUS - anaemia, thrombocytopenia and acute renal failure. Haemoglobin dropped from 11.5 to 6.5 g/dL. Platelets decreased from 152 to 6 x 10^9/L. Peripheral blood film showed microspherocytes and marked red blood cell fragmentation, suggestive of microangiopathic haemolysis. His creatinine rose from 39 to 90 umol/L, and urea from 6.9 to 15.7mmol/L.

Blood cultures grew streptococcus pneumoniae, serotype 19A, sensitive to ceftriaxone and vancomycin. This serotype was not covered by the 7-valent vaccine he received 2 years earlier.

A family conference was held with the parents. When informed that the patient will require blood product transfusions and haemodialysis in addition to intravenous antibiotics, the mother accepted placidly. She even commented: "You are all more worried than me!"

Transfusions
The patient was transfused with "washed" red blood cell concentrate and plasma-reduced platelets for his anaemia and thrombocytopenia respectively.

Dialysis
He underwent continuous veno-venous haemodialysis for 10 days in view of his acute renal impairment and fluid overload state. A Tenckhoff catheter was inserted thereafter and peritoneal dialysis was commenced in anticipation of prolonged renal recovery.

Respiratory support
His fluid overload state also resulted in pulmonary oedema, which, coupled with ongoing pneumonia, led to significant respiratory distress. He was intubated and also underwent thoracoscopic decortication of his right lung empyema. A chest tube was inserted for continued drainage of pus post-operatively.

Antibiotics
He had a persistent fever despite being on intravenous ceftriaxone. He was subsequently placed on intravenous vancomycin followed by piperacillin-tazocin and then meropenem. Endotracheal tube culture grew sternotrophomonas sensitive to sulfamethoxazole and trimethoprim (Bactrim), which was then added on to the antibiotic regimen. Pleural fluid, empyema culture and repeat blood cultures did not yield any bacterial growth.

Progress
The patient improved and was extubated on day 17 of illness. He was transferred to a general ward after 19 days in the PICU.

His antibiotics were converted to oral cefuroxime after completing 11 days of intravenous meropenem and 2 weeks of oral Bactrim. He completed a total of 33 days of antibiotics.

His fever was on a downward trend. Inflammatory markers were also downtrending and chest X-ray showed resolving consolidation and effusion. His chest tube was removed.

The Tenckhoff catheter was leaking on day 10 of peritoneal dialysis and had to be removed. However, his renal function showed continuing improvement. He produced good urine output with intravenous frusemide. Serum creatinine improved from 334 to 55umol/L. Enalapril was started for renal protection.

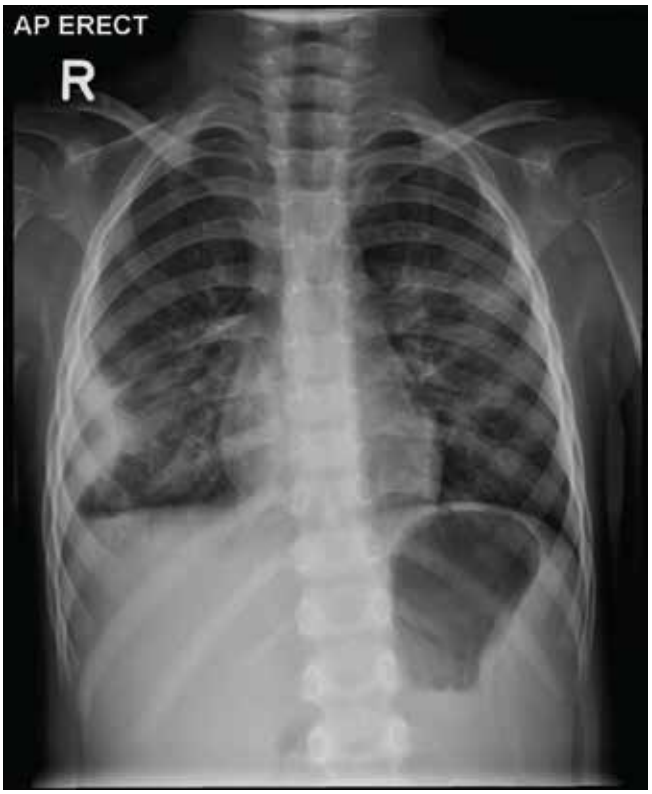
Discharge and follow-up
The patient was discharged well after 37 days in hospital. Reviewed in the outpatient clinic 1 week later, he was chatty, active and ambulant. Urine output was normal. A repeat chest X-ray (Figure 3) showed an almost resolved consolidation and no effusion was seen.

One month later, his haemoglobin was 9.5 g/L and his serum creatinine was stable at 65umol/L.

GAINING INSIGHT: WHAT ARE THE ISSUES?

This case triggered several issues:
i) What are the factors that could account for the mother reacting so calmly in the face of a grave disease that required prolonged and intensive treatment?
ii) What are the pathophysiology, clinical features, treatment and prognosis of SP-HUS?
iii) How do we prevent this condition and what is the choice of first-line antibiotics to treat community acquired pneumonia in children?

FIGURE 3. CHEST X-RAY OF PATIENT ONE WEEK AFTER DISCHARGE FROM HOSPITAL



STUDY THE MANAGEMENT: HOW DO WE APPLY THE INSIGHTS IN OUR CLINICAL PRACTICE?

Patient's mother's reaction

The patient's mother was unusually calm even after being told that her son needed intensive care. This response is even more significant considering that the patient is her only son. During the family conference, the team paused at frequent intervals to allow for questions. She mainly sought confirmation of what she understood. She did not at any point ask how the complication could have been prevented, and seemed to accept her son's condition as it was.

There were several reasons that could account for the mother's placidness. Seeing how she readily accepted management decisions, she probably had confidence in the team of doctors looking after her child. Another explanation would be that she could not comprehend the gravity of the situation, or that she was in a state of denial. My management of this patient was limited to two days in the general ward as he was transferred to intensive care thereafter. In my limited interactions with the parents, I found the mother well spoken, articulated and highly educated. It was unlikely she could not grasp the severity of the situation. Her husband was the silent type but was constantly by her side. He probably was her source of emotional support, simply by just being there. It may have helped her handle the bad news better.

In a cohort study by Jee RA et al,[1] coping strategies of parents in a paediatric intensive care unit in the UK were evaluated. It was found that the main coping strategies employed by parents were related to trust, assurance, and believing in positive outcomes. In this case, it could be her trust in the medical team and her belief in positive outcomes which led to her calm response.

A qualitative study was done on American physicians' experiences in communicating with families of children who suffer from acute life-threatening conditions[2]. This study revealed some helpful points which we can practise. Most families wanted timely and accurate information about the child's condition, and a private room where they can express their feelings or grieve. Start off by finding out the parents' level of understanding, and ask if they have any questions first. Bring them up to date using terminology appropriate to their level. Stage the delivery of bad news, giving it in increments depending on how much the family can take. It may have to take place over multiple meetings. Do not give false hope. The important role of a nurse or social worker to provide psychosocial, emotional and spiritual support was also emphasised.

Haemolytic uraemic syndrome

This is a clinical syndrome characterised by microangiopathic haemolytic anemia, thrombocytopenia and progressive renal failure. It predominantly affects children and has a peak incidence between six months and four years of age[3]. The most frequent cause is Shiga toxin-producing Escherichia Coli O157:H7[4] which is associated with bloody diarrhoea.

HUS can also be caused by invasive streptococcus pneumoniae infection, as demonstrated by this case. This variant is uncommon and involves 5% of all cases of HUS in children. The incidence of HUS following invasive pneumococcal infections is estimated to be 0.4 to 0.6%[5,6].

Pathophysiology

SP-HUS is due to an antigen-antibody reaction. The Thomsen-Friedenreich (TF) cryptantigen is a component of the surface structure of erythrocytes, platelets and glomerular endothelial cells. This antigen is normally hidden by neuraminic acid.

Pneumococci produce neuraminidase which cleaves neuraminic acid, exposing the TF antigen. Preformed host IgM antibodies then bind the TF antigen and initiate a cascade of events leading to autoimmune complement-mediated destruction of the affected cells, resulting in anaemia, thrombocytopenia and glomerular endothelial cell damage which characterises HUS.[4]

All serotypes of streptococcus pneumoniae have neuraminidase activity. Different serotypes may produce varying amounts of neuraminidase, thereby influencing the likelihood of a patient's developing HUS.[4]

Clinical Features

Features of pneumococcal HUS usually develop 7 to 9 days after initial infection.[7] Patients develop oligo-anuria and are found to have elevated plasma creatinine secondary to renal

failure. They have generalised oedema from the resultant volume overload. The patient may progress to end-stage renal failure in the long term.

Other key features in the acute stage are generalised pallor due to anaemia, and petechiae due to thrombocytopenia. Anaemia and volume overload will stress the heart. The patient may develop cardiac failure which can manifest as pulmonary oedema, hepatomegaly from liver congestion as well as ascites from third-spacing.

Treatment Overview

Management revolves around controlling the infection with antibiotics, as well as instituting supportive measures for anaemia and acute renal failure. Vancomycin and an extended spectrum cephalosporin should be started for treatment of invasive pneumococcal infection.[8] A specific antibiotic can be used once sensitivities are available. Dialysis is usually instituted if patients have prolonged periods of anuria or electrolyte abnormalities. Any type of dialysis - peritoneal, haemodialysis, continuous renal replacement therapy - may be used. Red blood cell transfusions are commonly administered to patients with symptomatic anaemia. These patients are usually tachycardic and in cardiac failure. Platelets may also be transfused if the patient shows signs of petechial haemorrhage, gum bleeding or epistaxis. Blood products have to be "washed" prior to transfusion to eliminate the pre-formed IgM antibodies which mediate TF antigen destruction. Other supportive measures include maintaining fluid and electrolyte balance and providing nutritional support. Feeding can be enteral or parenteral.

Prognosis

A PubMed literature search done using the key words "streptococcus pneumoniae", "haemolytic-uraemic syndrome" and "paediatric" produced 5 case series which were pooled, totalling 106 cases with known outcomes. The 106 cases were from a series from New Zealand (11)[9], Taiwan (20)[10], Hong Kong (5)[11], US (37)[12] and UK (43)[13], excluding 10 cases which did not have outcomes recorded. The pooled results showed full recovery in 29% of patients and mortality of 8.5%. 62.5% had renal, pulmonary, and neurological complications.

We note that renal dysfunction occurred in both Asian and Western patient groups but a smaller percentage of the Asian patients required dialysis. Months after the acute illness abated, Asian patients had a better renal prognosis than their western counterparts in terms of chronic renal impairment and dialysis requirement. However, as the follow-up period and data on types of complications were different in each of the studies, no clear unifying conclusion can be drawn with regards to long-term prognosis of SP-HUS.

DISCUSSION

This patient received the 7-valent pneumococcal conjugate vaccine (PCV7) 2 years earlier. However, invasive pneumococcal disease produced by non-PCV7 serotypes, particularly 19A, have been increasing in prevalence and antibiotic resistance in the past decade.[14] A newer vaccine containing 13 conjugate components (PCV13) was developed to expand serotype coverage and to address the disease burden caused by emerging serotypes. PCV 13 covers 6 additional strains of serotypes 1, 3, 5, 6A, 7F and 19A. It has been incorporated into our national immunisation program.

In the event that a child <24 months of age received ≥1 dose of PCV7, the immunisation series should be completed with PCV13. Children aged 14 to 59 months who are fully vaccinated with PCV7 should receive a single "catch up" dose of PCV13.[15]

Early diagnosis of community acquired pneumonia is not easy. A high index of suspicion is needed. Suspect pneumonia when URTI symptoms, such as cough, rhinitis or vomiting, which develop over one to several days are later followed by high fever. However, clinical presentations can be misleading. In a study by Toikka et al, it was noted that as many as one-fourth of the patients do not have any respiratory symptoms.[16] 38% of patients presented with gastrointestinal symptoms. To help in diagnosis, a chest radiograph should be obtained, especially from children with high fever (≥39deg C) and ill appearance.

Based on guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America[17], amoxicillin should be used as first-line therapy for previously healthy, appropriately immunised infants and preschool children with mild to moderate community-acquired pneumonia suspected to be of bacterial origin. Alternatives would be a second or third-generation cephalosporin, or levofloxacin. For patients allergic to penicillins or cephalosporins, alternatives are levofloxacin and clindamycin. Levofloxacin is the preferred antibiotic for streptococcus pneumoniae resistant to penicillin.

We also need to suspect antibiotic failure early and SP-HUS if the patient does not improve. Based on Toikka et al's study, most pneumonia patients become afebrile within 24hours after starting antibiotics. Should the patient fail to respond to therapy after a day or two, we need to consider antibiotic resistance or invasive pneumococcal disease, which can lead to SP-HUS. We must keep in mind that SP-HUS can develop 3 to 13 days after a pneumococcal infection,[4] hence the importance of close follow-up. Have a high index of suspicion in a child with pneumonia who develops signs of anaemia, fluid overload and/or thrombocytopenia, which are hallmarks of SP-HUS. It was fortuitous that the mother of this child did not do doctor hopping but brought the child back for repeat consultation at the same point of care 3 times.

CONCLUSION

A disease less often encountered and with a threat to life generates great worry amongst the medical team. Such challenging episodes leave an indelible impact and physicians who managed these cases will be better primed to diagnose and

manage medically challenging situations in the future.

The points of note in this case study are:
1) Haemolytic uraemic syndrome is a rare but potentially fatal complication of streptococcal pneumonia infection. A high index of suspicion for such an occurrence is needed.
2) Symptoms and signs suggestive of SP-HUS in a patient with pneumonia are: remaining unwell despite use of antibiotics, decreased urine output, tachycardia, a gallop rhythm, pallor, petechiae, peripheral oedema. Laboratory investigations done at this stage will show anaemia, thrombocytopenia and elevated creatinine.
3) Communication with parents of a paediatric patient is important. Parents want timely and accurate information. Bad news has to be given in increments or over multiple meetings, depending on how much the family can take. Trust in the team, reassurance and believing in positive outcomes are major coping mechanisms of parents.
4) Children aged 14 to 59 months who are fully vaccinated with PCV7 should receive a single "catch up" dose of PCV13.
5) Amoxicillin should be used as first-line therapy for appropriately immunised infants and preschool children with mild to moderate community-acquired pneumonia suspected to be of bacterial origin. Levofloxacin is the preferred alternative for those with penicillin allergy.

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The patient's mother has given permission for the authors to publish the X-ray images in this article.

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