Complete Renal Recovery in Pediatric Patient with *Streptococcus pneumoniae*-Associated HUS: A Case Report and Literature Review

Elizabeth Mancuso[1], Jeanvieve Cannon[1], Bree C. Kramer[2], Michael Bowler[2], Oscar G. Gómez-Duarte[3], Beverly Schaefer[4], Wayne R. Waz[5], Xiaoyan Wu[5*]

[1]Department of Pediatrics, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, State University of New York, Buffalo, NY, USA

[2]Division of Pediatric Critical Care, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, State University of New York, Buffalo, NY, USA

[3]Division of Pediatric Infectious disease, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, State University of New York, Buffalo, NY, USA

[4]Division of Pediatric Hematology and Oncology, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, State University of New York, Buffalo, NY, USA

[5]Division of Nephrology, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, State University of New York, Buffalo, NY, USA

***Corresponding author:** Xiaoyan Wu, Department of Pediatric Nephrology, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, 1001 Main Street, Buffalo, NY 14203, USA

Abstract

Hemolytic uremic syndrome caused by invasive pneumococcal disease (Sp-HUS) is rare in children and adolescents, has a high mortality in the acute phase and is often complicated by long term renal sequelae. Here we report a 22-month-old female with no significant past medical history who was initially admitted for severe streptococcal pneumonia, which ultimately progressed to acute kidney injury and hemolytic anemia. Broad functional complement analysis showed low C3 and C4, and genetic complement analyses were negative. Coagulation studies were examined at the time of HUS diagnosis. The presence of normal fibrinogen levels associated with findings consistent with HUS was used to rule out disseminated intravascular coagulopathy (DIC). The patient required hemodialysis and received plasmapheresis. The patient did not receive C5 blockade. During a follow up time of 12 months, the patient showed no signs of renal sequelae.

Introduction

Thrombotic Microangiopathy (TMA) is a clinical-pathological syndrome characterized by microangiopathic hemolytic anemia, thrombocytopenia and acute kidney injury. Hemolytic Uremic Syndrome (HUS) is a heterogeneous group of diseases that result in a common feature of TMA. While most cases of HUS in the pediatric population are associated with an antecedent diarrheal illness caused by Shiga-toxin producing *Escherichia coli* (STEC), there are other, non-diarrheal, infections that lead to HUS. [1-3] One such infection is *Streptococcus pneumoniae,* which can lead to pneumococcal HUS (Sp-HUS). Pneumococcal HUS accounts for approximately 5% of the total cases of HUS in the pediatric population, with the highest prevalence found in children less than two years of age. [1-4] The incidence of HUS complicating invasive pneumococcal infections is estimated to be 0.4 to 0.6%. [3,5,6] The clinical features typically occur 3 to 13 days after the onset of the acute pneumococcal infection. [6,7] When compared with STEC HUS, patients with Sp-HUS are typically younger and usually have higher morbidity and mortality. Historically, Sp-HUS has been characterized with a severe acute disease course resulting in prolonged hospital admissions, with patients requiring frequent hemodialysis and multiple transfusions of platelets and Packed Red Blood Cells (pRBCs). Additionally, there is a higher incidence of long-term kidney and liver injury associated with Sp-HUS [8].

The exact pathophysiology of Sp-HUS has not yet been determined, however, the Thomsen-Friedenreich (T) antigen is known to play a crucial role. [9-11] The T-antigen is a component of the surface structure of erythrocytes, platelets and glomerular endothelial cells and is normally hidden by neuraminic acid. Neuraminidase, produced by *S pneumoniae*, cleaves N-acetylneuraminic acid from glycoproteins on the plasma membranes resulting in exposure of the T-antigen on these cells. Preformed anti-T antigen IgM antibodies can subsequently interact with the exposed T-antigen, initiating the cascade of events that leads to Sp-HUS. Additionally, abnormalities in the alternative complement pathway may contribute to the course of Sp-HUS. [12,13] Evidence demonstrates that pneumococcal neuraminidase can also disrupt Factor H (an important inhibitor of the alternative complement pathway) and impair its ability to effectively bind to host cells. This loss of function can then lead to indiscriminate complement activation and host cell injury. [14] In fact, complement (C3) and factor H have been found to be lower in patients with Sp-HUS. Further evidence to support the role of the complement system in HUS can be based on the effectiveness of the complement C5 inhibitor, eculizumab, as a treatment modality in some cases. [12] Here we report one case of Sp-HUS in a female patient who was diagnosed at age of 22 months. Her primary organ manifestations were respiratory failure due to pneumonia and acute kidney injury. Her invasive pneumococcal infection was treated with IV antibiotics and HUS was managed with hemodialysis and plasmapheresis. Broad functional and genetic complement analyses were negative, and she did not receive anti-complement treatment. Ultimately, she survived the acute phase of Sp-HUS and had complete renal recovery.

Case Presentation

A previously healthy 22-month-old female presented to the emergency department of a hospital in the northeastern United States with respiratory distress. Four days prior to presentation, she presented to the same emergency department for one day of fever and rash and was discharged on the same day with a diagnosis of viral upper respiratory infection. The patient was up-to-date on her vaccinations and had no history of sick contacts. In the emergency department, her temperature was 38.9°C, pulse was 212 beats per minute, blood pressure was 83/44 mmHg, respiratory rate was 68 breaths per minute, and oxygen saturation was 98% on room air. Her physical examination was remarkable for tachypnea with accessory muscle use and diminished breath sounds on the left side. CXR demonstrated left sided pneumonia with effusion as well as consolidation of the right upper lobe (Figure 1A). Blood cultures were obtained and the patient received IV ceftriaxone and vancomycin for community acquired pneumonia. High flow nasal cannula was initiated due to moderate respiratory distress. She had decreased urine output despite fluid resuscitation. She had no signs of active bleeding. She subsequently progressed to respiratory failure within hours and was intubated before being admitted to the Pediatric Intensive Care Unit (PICU) for management of acute respiratory failure and sepsis in the setting of bilateral pneumonia. On admission labs were significant for hemolytic anemia with a hemoglobin of 5.8 g/dL, LDH of 4,906 unit/L (nl 155-345 unit/L), haptoglobin of 12mg/dL (nl 30-200 mg/dL) (Figure 2, upper); thrombocytopenia with platelets of 10×10^9/L (Figure 2, left lower), and acute kidney injury with a serum creatinine of 1.68mg/dL, BUN of 59mg/dL (Figure 3). Of note, the patient had a white count of 8.5×10^9/L and moderate schistocytes on peripheral smear (data not shown). Her UA was significant for 1+ protein (30mg/dL) without gross hematuria. DIC panel was significant for a prolonged PT of 17.3 sec (nl 11-15 sec), prolonged aPTT of 71.1 sec. (nl 25-34 sec), elevated fibrinogen of 573mg/dL (nl 200-470 mg/dL), and D-Dimer of 5.31mcg/mL (Figure 2, right lower).
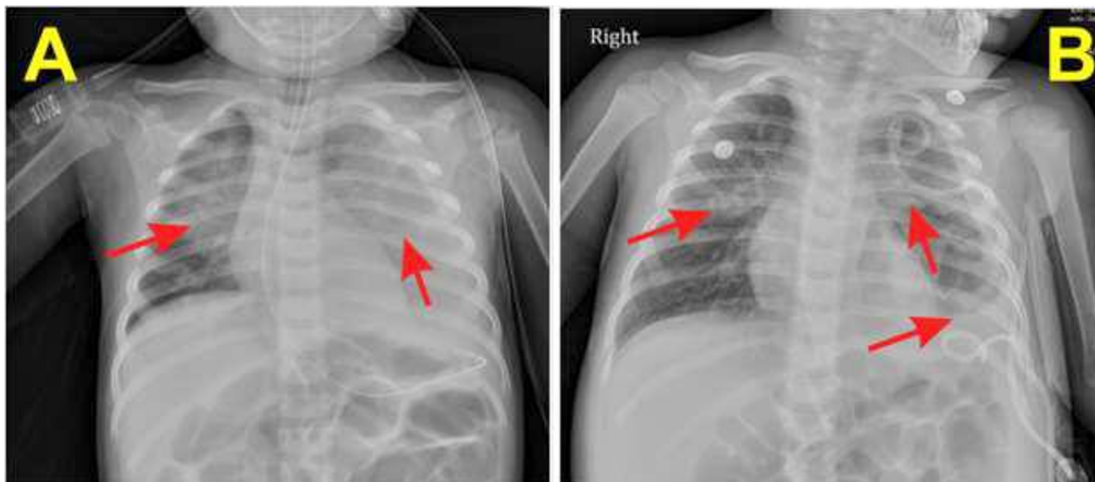
Figure 1: CXR on admission (A) and day 15 (B) of the hospitalization. **A**. There are bilateral infiltrates and left pleural effusion (red errors). **B**. There is a large cavitary lesion in left lower lobe of the lung indicating necrotizing pneumonia in the setting of *Streptococcus pneumoniae* infection (blood culture was positive on admission & tracheal aspirate was positive on hospital day 2) (red errors). Antibiotics (Azithromycin, vancomycin and ceftriaxone) were initiated on admission; azithromycin was given one dose, and vancomycin was discontinued on hospital day 4. Ceftriaxone was continued until hospital day 18 at which time the patient was started on amoxicillin. The *S. pneumoniae* strain was susceptible to all antibiotics tested including penicillin, clindamycin and erythromycin. Patient remained on amoxicillin for approximately 2 weeks to complete one month of antibiotics therapy.
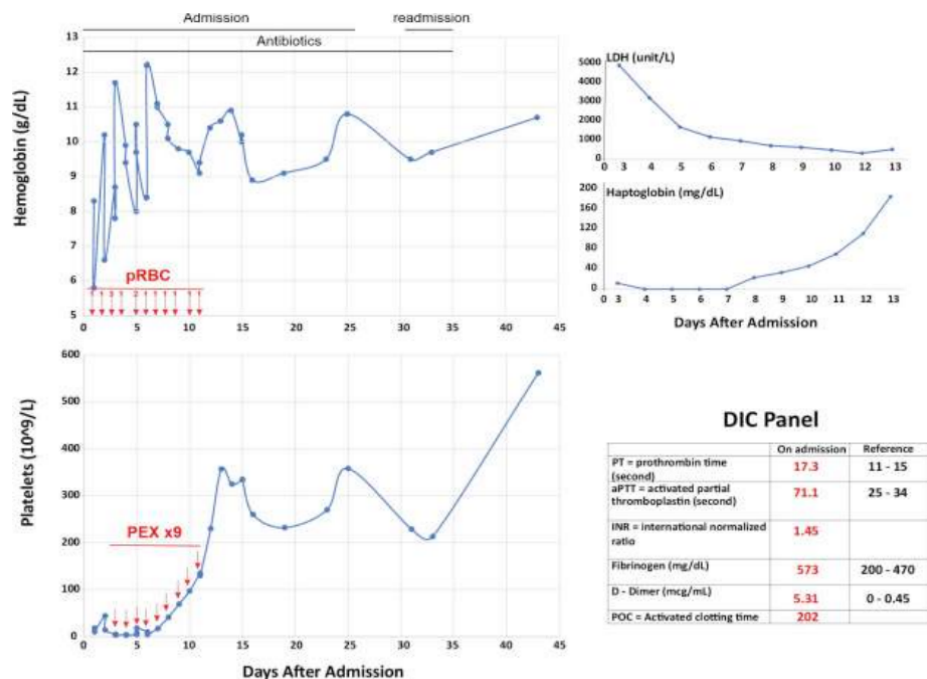
Figure 2: Changes in hemoglobin (left upper) and platelets (left lower) throughout the patient's hospital course. As indicated, the patient had severe anemia which required frequent pRBC transfusions (left upper). High LDH and low haptoglobin suggested hemolytic anemia (right upper). Patient also had thrombocytopenia which improved with PEX (left lower) with a total of 9 treatments. After one month of therapy, the patient's hemoglobin and platelet levels started trending upward. Coagulation Panel showed prolonged PT, prolonged aPTT, high INR and high D-Dimer, in the presence of normal level of fibrinogen level, the finding was consistent with Sp-HUS (right lower). Coomb test was negative. The patient was discharged home after 25 days of hospitalization, and readmitted for 4 days for recurrent fevers.
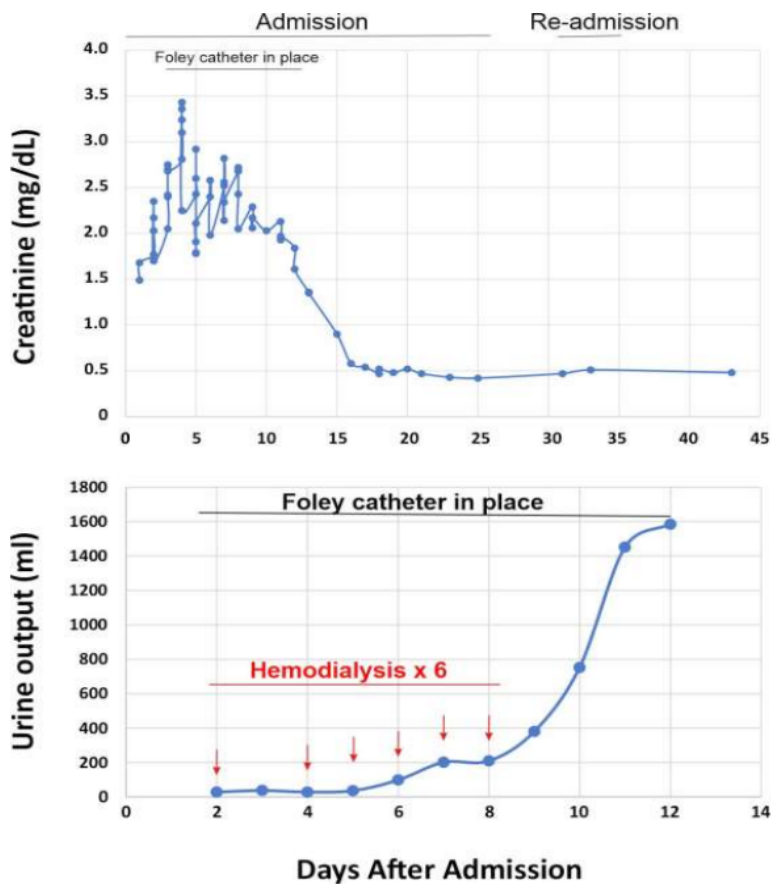
Figure 3: Changes in serum creatinine (upper) and urine output (lower) throughout the patient's hospital course. As indicated, the patient was anuric on admission. Her serum creatinine continued rising after admission at which time hemodialysis was initiated. After a total 6 hemodialysis treatments, her urine output improved and her foley catheter was removed shortly after followed by her hemodialysis catheter being removed. After one month of therapy, her kidney function returned to normal and remained normal during her re-admission to the hospital.

Given the patient's hemolytic anemia, thrombocytopenia, anuric Acute Kidney Injury (AKI), and elevated PT, PTT, fibrinogen, and D-Dimer, a working diagnosis of Thrombotic Microangiopathy (TMA) was considered. On hospital day 2, labs were sent for ADAMTS13, C3, C4, TMA panel and infectious panel. These results were remarkable for an ADAMTS13 activity of 24.1%, C3 of 43mg/dL (nl 80-175 mg/dL), and C4 of 2.9mg/dL (nl 14-40 mg/dL). Low complement levels (C3 and C4) and an ADAMTS13 activity >10% suggested a working diagnosis of hemolytic uremic syndrome (HUS). A TMA genetic panel was then sent on hospital day 5 to confirm the diagnosis. A repeat ADAMTS13 on hospital day 7 and 8 resulted 17% and 17.7% respectively (Table 2). On hospital day 3 blood culture sent on admission returned positive for *Streptococcus pneumoniae*, pansensitive. Again, on hospital day 6, tracheal aspirate culture sent on hospital day 2 returned positive for *Streptococcus pneumoniae* and a diagnosis of *Streptococcus pneumoniae* HUS was confirmed (Table 1). Vancomycin, which was initiated on admission, was discontinued on hospital day 4**.** Ceftriaxone was continued until hospital day 18**,** at which time patient was started on amoxicillin and she remained on amoxicillin for 2 weeks to complete a course of one month therapy. The patient had ongoing fevers and respiratory failure. On hospital day 5, the patient underwent IR guided drainage of her left lung pleural effusion with chest tube placement. A second chest tube was placed on hospital day 8 after a multiloculated pleural effusion was found on ultrasound of the chest. The patient was extubated on hospital day 11 to high flow nasal canula and was gradually weaned to room air. A chest CT on hospital day 13 showed extensive cavitation consistent with necrotizing pneumonia involving the left lower lobe and a cavitation with an air-fluid level within the posterior right upper lobe. The patient's chest tubes were removed on hospital day 15 after a significant decrease in drainage was observed and pulmonology was consulted for further monitoring. A repeat CXR on hospital day 15 showed cavitary pneumonia as a result of severe necrotizing pneumonia in the setting of streptococcal pneumonia infection (Figure 1B). For treatment of anemia, she received multiple Packed Red Blood Cell (pRBC) transfusions while in the PICU, with gradual normalization of her hemoglobin (Figure 2, left upper). Plasma Exchange (PEX) with 5% albumin at 1.5x plasma volume was initiated on hospital day 3 in order to treat the patient's thrombocytopenia. She underwent a total of 9 PEX treatments with the last treatment being on hospital day 11 (Figure 2, left lower). Nephrology was consulted and hemodialysis was initiated on hospital day 2 for anuric AKI. The patient underwent a total of 6 hemodialysis treatments with her last treatment being on hospital day 8 with resolution of her AKI as seen by a gradual improvement in her creatinine along with an increase in urine output (Figure 3).

Bacterial Testing		
Blood culture	*Streptococcus pneumoniae*	**positive**
Tracheal aspirate culture	*Streptococcus pneumoniae*	**positive**
Viral Testing		
	Hepatitis B Surface Ag	Negative
	Hepatitis B Core Ab	Negative
	Hepatitis B Surface Ab	>1000
	Hepatitis C Ab	Non-Reactive
	Pleural Fungal Culture	Negative
	Pleural Acid-Fast Bacilli	Negative
	Rhinovirus PCR	Negative
	Influenza A PCR	Negative
	Influenza B PCR	Negative
	Respiratory Syncytial Virus PCR	Negative
	Parainfluenza virus 1	Negative
	Parainfluenza virus 2	Negative
	Parainfluenza virus 3	Negative
	Parainfluenza virus 4	Negative
	Adenovirus PCR	Negative
	Metapneumovirus PCR	Negative
	SARS COV2 PCR	Negative

Table 1: Infectious panel. As indicated, blood culture and tracheal culture were positive for *Streptococcus pneumoniae*. Repeat cultures were negative indicating antibiotics therapy was effective. Viral panels were negative.

		Reference
ADAMTS13 Activity (%)	16.5-24.1%	<10% TTP
		>10% HUS
ADAMTS13 Antibody	2-6	
Complements		
C3 (mg/dl)	43	80-175
C4 (mg/dl)	< 2.9	14-40
TMA genetic panel	*ADAMTS13*	Negative
	C3	Negative
	CD46	Negative
	CFB	Negative
	CFD	Negative
	CFH	Negative
	CFHR1	Negative
	CFHR3	Negative
	CFHR5	Negative
	CF1	Negative
	DGKE	Negative
	PLG	Negative
	TKBD	Negative

Table 2: TMA panel. The ADAMTS13 activity, ADAMTS13 antibody, complements during hospitalization, and TMA genetic panel are shown. An ADAMTS13 activity less than 10% is suggestive of TTP while an ADAMTS13 activity greater than 10% is significant for atypical or typical hemolytic uremic syndrome. Patient described in the case had 16.5-24.1% of ADAMTS13 activity and 2-6 of ADAMTS13 antibody, consistent with streptococcal pneumoniae HUS. Though complements (C3 and C4) were low, the TMA genetic panel was negative. The patient did not receive Eculuzimab as treatment for Sp-HUS.

For hypertension development, initial Systolic Blood Pressure (SBP) was elevated at 137 mmHg due to fluid overload and she started on furosemide. On hospital day 12, Isradipine was added for persistent SBP as high as 168 mmHg. On hospital day 17, clonidine was added for one week for better blood pressure control. On hospital day 19, both furosemide and Isradipine were discontinued. And patient started on amlodipine on hospital day

20. Amlodipine was continued on for 3 months (Figure 4 upper). At 7 months of follow up, her blood pressure has remained without antihypertensive medications (Figure 4 lower). The patient had significant improvement of her hemolytic anemia and thrombocytopenia. She also had a substantial recovery of her renal function with improved urine output. She was transferred from the PICU to the floor in stable condition on hospital day 18 at which time her antibiotic therapy was transitioned to oral amoxicillin. The patient was discharged on hospital day 26 with improved clinical status, complete resolution of her fevers, and normalization of her platelet count (Figure 2). Patient was followed up in clinic with ID and nephrology. At 12 months of follow up, there was no disease recurrence.
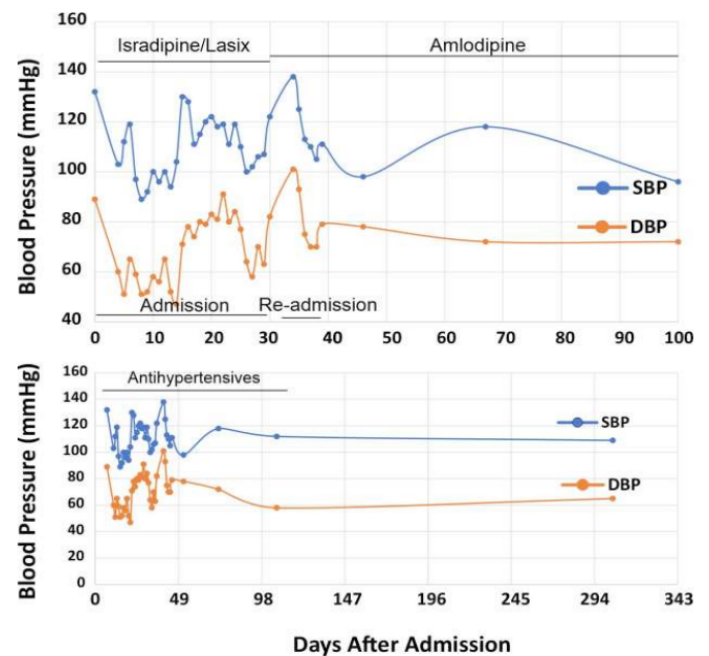

Figure 4. Change of blood pressure during and after hospitalization. As indicated, initial systolic blood pressure (SBP) was elevated due to fluid overload at which time furosemide started. On hospital day 12, Isradipine was added for persistent hypertension. On hospital day 17, clonidine was added for one week for better blood pressure control. On hospital day 19, both furosemide and Isradipine were discontinued. And patient started on amlodipine on hospital day 20. Amlodipine was continued on for 3 months (Figure 4 upper). She weaned off oral amlodipine after 3 months, and blood pressure has remained normal without antihypertensive medications (Figure 4 lower).

Discussion

HUS as a complication of invasive pneumococcal infection has been recognized for over 50 years. [15] Sp-HUS is a rare and under-recognized condition that mainly occurs in young children. Early diagnosis and treatment are essential due to the

potential to significantly improve morbidity and mortality. Here we report a case of pneumococcal pneumonia and Sp-HUS with associated Thrombocytopenia-Associated Multiple Organ Failure (TAMOF) in a 22-month old girl. She was successfully treated with IV antibiotics, plasmapheresis, and hemodialysis with complete resolution of renal recovery. Despite a prolonged prothrombin time (PT) and partial thromboplastin time (aPTT) at the time of diagnosis, an elevated fibrinogen level effectively ruled-out DIC as the underlying etiology. Pneumonia, particularly when complicated by empyema, is the most frequent antecedent illness associated with Sp-HUS, with meningitis and bacteremia following thereafter. [2,6,8,16] Copelovich et al reviewed 85 cases of pediatric Sp-HUS and identified that 72% were associated with pneumonia and/or empyema and 29% with meningitis.[6] Other, more recent, studies have confirmed this trend [2,8,16] , including a national surveillance study completed in the United Kingdom. It found that, between 2006 and 2016, 57% of children with Sp-HUS presented with pneumonia (84% of which had empyema) 25% with meningitis and 15% with bacteremia.[2] It has been postulated that suppurative infections, such as empyema, have higher bacterial loads, which may increase the risk of developing Sp-HUS [3,8,16]

The diagnosis of Sp-HUS remains a significant challenge due to the lack of consensus amongst experts of a definitive diagnostic strategy and its significant clinical overlap with DIC and pneumococcal septic shock. [6,8,17,18] Authors disagree on the extent of testing required to confirm the diagnosis and while some are satisfied with the simple association of HUS in the context of a pneumococcal infection, others argue that additional diagnostic evidence is required to conclusively prove secondary HUS, rather than DIC or sepsis, is the underlying etiology. Further complicating the diagnostic complexity is that HUS must be categorized based on whether the underlying etiology is related to complement pathway dysregulation or not. Infection-related "typical" HUS denotes HUS in the context of STEC, *S. pneumoniae* or influenza A/H1N1 infections. "Atypical HUS" is a broad category which denotes HUS related to any other underlying cause. Within the atypical category there is "primary" HUS, which specifies HUS caused by underlying complement dysregulation related to gene variants, and "secondary" HUS, which occurs when HUS is triggered other causes including infections, malignancy, drugs, and autoimmune diseases. There may be an element of overlap of these categories, in which genetic-related complement dysfunction may be triggered by infections, like COVID and STEC. Whether Sp-HUS belongs to the same spectrum of complement-mediated HUS remains unclear and is currently an active area of research.

The Canadian Pediatric Surveillance program published the first diagnostic strategy for Sp-HUS in 2002, which required tissue evidence of TMA from renal biopsy or autopsy to confirm the diagnosis. [19] This was considered neither practical nor useful in the clinical setting and, as such, other experts have developed alternative definitions of Sp-HUS, which utilize different diagnostics as evidence of T-antigen activation including the direct

Coombs test and the peanut lectin agglutination test. Demonstration of T-antigen presence by peanut agglutinin test is 86% sensitive and 57% specific with positive predictive value of 76%. [17,20] Huang et al determined that T-antigen activation occurs prior to the development of anemia or thrombocytopenia in Sp-HUS and, thus, recommend peanut agglutinin testing immediately upon suspicion or diagnosis of an invasive pneumococcal infection. [20] This test, however, is not routinely available at most clinical laboratories and in our case, peanut lectin agglutination test was not performed. The positivity of direct Coombs test among children with Sp-HUS varies and its specificity remains unclear. [17] The direct Coombs test detects antibodies bound to erythrocytes and is positive in up to 90% of cases of Sp-HUS. [11] There is limited evidence, however, on the incidence of a positive Coombs test in the setting of non-HUS forms of pneumococcal infections.

The management of Sp-HUS typically includes treatment of the invasive pneumococcal infection with an extended spectrum cephalosporin and vancomycin and, otherwise, involves predominately supportive care including transfusions and hemodialysis to correct the anemia, thrombocytopenia and AKI, respectively. [6,12] Early detection and rapid initiation of antibiotics decrease mortality. We initiated therapy with combination of vancomycin and cephalosporin to provide broad antibacterial coverage. Therapy was directed according to cultures and sensitivity and vancomycin was discontinued on hospital day 4. The patient remained on ceftriaxone until hospital day 18 and, upon, discharge, was continued on amoxicillin to complete a total of 4 weeks of therapy. Given that anti-T-antigen IgM antibodies are fundamental in the pathogenesis of Sp-HUS, administration of additional preformed antibody, in the form of Fresh Frozen Plasma (FFP) or unwashed blood products, should be avoided. [6,12] Since there was a need for platelet transfusion and red blood cell concentrate, we used Dextran-washing to remove plasma from blood products. The washed transfusion products were used for management of the anemia and thrombocytopenia (Figure 2). FFP should only be administered in cases of active bleeding and was not required in our case. She received total 14 of pRBC transfusion and multiple platelet transfusions (Figure 2).

The removal of neuroaminidase by plasma exchange is hypothetically indicated. However, plasma exchange is controversial since IgM antibody against the T-antigen may result in possible increased polyagglutination and aggravation of the microangiopathic phenomenon. [16] Use of plasmapheresis has not demonstrated significant improvement in outcomes in cases of Sp-HUS. In the literature there are two case reports which demonstrated successful use of plasmapheresis in the context of Sp-HUS. [21,22] Our case provides further evidence in favor of the use of plasmapheresis in Sp-HUS, as our patient received a total of 9 treatments with subsequent significant improvement in her thrombocytopenia (Figure 2). Eculizumab is a C5 inhibitor, and it is a humanized monoclonal IgG that binds to and blocks the cleavage of the C5 complement protein, thereby disrupting

the formation of the membrane attack complex. [12] While its use has been successful in the management of atypical HUS, in which complement overactivation plays a major role, its utility in Sp-HUS has not been well defined. In our case, hypocomplimentemia was found initially on admission, but given a negative genetic TMA panel (Table 2), the utility of eculizumab in this case was less clear and was why its use was ultimately avoided. In cases of infection-driven HUS where hematologic remission is not achieved despite treatment of the underlying disease, anti-C5 therapy may be considered.

Long-term morbidity and mortality are thought to be worse in Sp-HUS than STEC HUS, although data obtained are variable. Mortality rates are reported as 12 to 15%, however, various studies support the notion that the site of infection plays a significant role in the fatality of Sp-HUS, with meningitis incurring the highest risk of death. [6,16,23] Copelovich et al report that 88% of deaths in Sp-HUS occurred in those with meningitis and noted a mortality rate of 37% in patients with pneumococcal meningitis complicated with HUS. By direct comparison, the mortality rate of Sp-HUS not associated with meningitis was 2%, which is comparable to that of STEC HUS. [6] Regarding the long-term sequelae of Sp-HUS, End Stage Kidney Disease (ESKD), hypertension, proteinuria and neurologic abnormalities are among the most common. [8,13,16] ESKD may occur in 10 to 16% of Sp-HUS [13] and it has been suggested that the need for acute dialysis for more than 20 days is the greatest risk factor, although evidence on this is scarce. [13,17] The patient in our case had acute kidney injury with anuria requiring hemodialysis. In addition, she required initiation of antihypertensive medications during the acute phase. Overall, she responded exceptionally well to the therapies and had complete renal recovery.

Conclusion

Sp-HUS is rare in children, but is accompanied by high mortality in the acute phase and is frequently complicated by long-term renal sequelae. The absence of a consistent definition and the lack of a specific supporting laboratory diagnostics may play a role in its under-diagnosis and late detection. From a practical point of view, Sp-HUS should be suspected when one or more of the following occurs in the context of HUS, - a toxic patient, pneumonia, meningitis or there is evidence of another invasive infection, a positive Coombs' test, hypocomplementemia, abnormal coagulation panel without a DIC. Based on these findings, we recommend aggressively treating *S. pneumoniae* infections along with supportive medical management.

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