Case Report

Haemolytic uraemic syndrome associated with Pseudomonas aeruginosa sepsis

Parameswaran Narayanan,† Rashi S. Rustagi,† Prabha Sivaprakasam,† Mahadevan Subramanian,† Sreejith Parameswaran,‡ Jharna Mandal§ and B. S. Kaplan¶

Correspondence
Parameswaran Narayanan
narayanan@jipmer.net

1Department of Paediatrics, Jawaharlal Institute of Postgraduate Medical Education and Research, Dhanvantari Nagar, Pondicherry 605006, India
2Department of Nephrology, Jawaharlal Institute of Postgraduate Medical Education and Research, Dhanvantari Nagar, Pondicherry 605006, India
3Department of Microbiology, Jawaharlal Institute of Postgraduate Medical Education and Research, Dhanvantari Nagar, Pondicherry 605006, India
4Department of Pediatrics, Division of Nephrology, The Children’s Hospital of Philadelphia, 34th Street and Civic Centre Boulevard, Philadelphia, PA 19104, USA

Haemolytic uraemic syndrome (HUS) is a recognized complication of infection with Shiga toxin-producing Escherichia coli (STEC) and Shigella dysenteriae type 1. Infections with other microorganisms, especially Streptococcus pneumoniae, have been cited as causes of HUS. In addition, influenza virus and other viruses may rarely be associated with this syndrome. A 2-year-old girl presented with severe Pseudomonas aeruginosa sepsis with renal failure and ecthyma gangrenosum. Further investigations revealed features of HUS. She was managed with antibiotics and other supportive measures including peritoneal dialysis, and subsequently made a full recovery. A possible role of neuraminidase in the pathogenesis of P. aeruginosa-associated HUS was proposed. This is the first reported case of P. aeruginosa sepsis leading to HUS.

Introduction

Haemolytic uraemic syndrome (HUS) is a recognized complication of infection with Shiga toxin-producing Escherichia coli (STEC) and Shigella dysenteriae type 1 infections and is characterized by microangiopathic haemolytic anaemia, thrombocytopenia and renal failure (Taylor, 2008). Other infectious agents reported as causing HUS include Streptococcus pneumoniae, Citrobacter freundii, Salmonella typhi, Epstein–Barr virus, H1N1 influenza A and other viruses (Albaqali et al., 2003; Copelovitch & Kaplan, 2008; Lee et al., 1998; Trachtman et al., 2011; Waters et al., 2007). We report the case of a 2-year-old girl diagnosed with Pseudomonas aeruginosa sepsis and shock who also developed features of HUS.

Case Report

A 2-year-old girl was brought to the emergency room with a 3-day history of fever, loose stools, decreased urine output and an altered sensorium. Facial puffiness was present for 2 days and respiratory distress for 1 day. Her stools were watery and foul smelling, but did not contain mucus or blood. Two days previously, her parents had noticed a swelling on the right upper thigh with discoloration of the overlying skin. There was no history of a rash or petechial spots, bleeding or seizures. Past history and family history were unremarkable. On examination, she was drowsy (Glasgow coma scale 11/15) and febrile (38.9°C) with bounding pulses, tachycardia (140 min⁻¹), tachypnea (40 min⁻¹) and hypotensive (80/40 mmHg). There was a tender, diffuse swelling with a bluish-black necrotic patch on the right thigh and buttock. There were no petechiae and there was no purpura. The provisional diagnosis was severe sepsis with septic shock, acute kidney injury and ecthyma gangrenosum. Investigations revealed anaemia (6.0 g dl⁻¹) and thrombocytopenia (25 000 μl⁻¹) with evidence of a microangiopathic haemolytic picture (schistocytes or fragmented erythrocytes present) on the peripheral blood smear. Serum lactate dehydrogenase was elevated (820 IU l⁻¹). Renal function was abnormal (blood urea concentration, 169 mg dl⁻¹; serum creatinine concentration, 3.9 mg dl⁻¹). The patient had a prolonged prothrombin time (international normalized ratio, 2.1) and a low fibrinogen concentration (30 mg dl⁻¹), but the test for fibrin degradation products was negative. Her liver enzymes were abnormal (alanine transaminase, 240 IU l⁻¹; aspartate aminotransferase,
380 IU $1^{-1}$). Stool culture was negative for enterohaemorrhagic \textit{E. coli}, \textit{Shigella} and \textit{Salmonella}. PCR for Shiga toxin gene (\textit{stx}) was also negative for the stool sample. The patient was resuscitated with isotonic fluids and inotropes for hypotension; antibiotics (ceftazidime, vancomycin and metronidazole) were added empirically for broad spectrum coverage in view of her poor general condition. Mechanical ventilation and peritoneal dialysis were initiated on day 1. Subsequently, the blood culture taken at admission grew \textit{P. aeruginosa} sensitive to ceftazidime, ciprofloxacin and amikacin, and the antibiotics regimen was changed to ceftazidime and ciprofloxacin. A total of 126 cycles of peritoneal dialysis were performed. The patient’s haemodynamic parameters improved by day 3 of admission, and after 4 days of peritoneal dialysis, her urine output started to improve. By day 10 of admission, her thrombocytopenia and microangiopathy had resolved and the serum creatinine concentration was normal by day 12. She was weaned off respiratory support by day 12 and was discharged after 3 weeks of hospitalization. One month later, she was doing well with normal renal parameters.

**Discussion**

Although STEC and \textit{S. dysenteriae} type 1 are still the most common agents causing HUS, many other organisms have been associated with this syndrome (Taylor, 2008). Bacterial infections caused by organisms like \textit{S. pneumoniae} and \textit{Salmonella} also cause HUS (Albaquili et al., 2003; Waters et al., 2007). Viral infections such as influenza virus, parvovirus, ECHO (enteric cytopathic human orphan) virus, coxsackie virus, cytomegalovirus and Epstein–Barr virus are associated with HUS (Cavagnaro & Barriga, 2000; Larke et al., 1983; Lee et al., 1998; Seward et al., 1999; Trachtman et al., 2011; Waizer et al., 1999). Our patient is perhaps the first case of \textit{P. aeruginosa} infection with the clinical manifestations of HUS in the medical literature.

The clinical presentation of our patient, especially the presence of erythema gangrenosum and septic shock, was highly suggestive of a pseudomonal sepsis, which was confirmed by isolation of \textit{P. aeruginosa} from the blood culture. Despite a history of loose stools, stool culture did not yield any enteric pathogens. However, diarrhoea is a common symptom in community-acquired pseudomonal sepsis (Huang et al., 2002). Our patient responded well to antibiotics and supportive management for septic shock in spite of her poor general condition at presentation. A diagnosis of HUS was first considered only after a few days of hospitalization.

The pathogenesis of HUS due to STEC and \textit{S. dysenteriae} type 1 is well characterized and is attributed to the production of Shiga toxin (Stx1 and Stx2). However, HUS resulting from pneumococcal infections occurs as a result of the bacterial enzyme neuraminidase. This enzyme cleaves the neumaminic acid from the cell surface thus exposing the Thomsen–Friedenreich antigen (TFAg) to pre-formed anti-TFAg IgM causing antigen–antibody binding and activation of an immune cascade that results in HUS (Copelovitch & Kaplan, 2008; Waters et al., 2007). The pathogenesis of HUS in influenza is not yet known although a role for a complement defect as a susceptibility factor has been postulated (Allen & Licht, 2011).

The enzyme neuraminidase may be involved in the pathogenesis of \textit{P. aeruginosa} sepsis causing HUS in our patient. \textit{Pseudomonas} is known to express a neuraminidase enzyme that can cleave α-2,3-linked sialic acids from glycoconjugates. This property can modify epithelial cells by exposing potential bacterial receptors thus contributing to the pathogenesis of respiratory infections (Leprat & Michel-Briand, 1980; Soong et al., 2006). We postulate that the neuraminidase of \textit{Pseudomonas} cleaves the neuraminic acid on erythrocytes and platelets thus exposing TFAg. This results in antigen–antibody interactions, thereby activating the inflammatory cascade. Further studies are required to confirm or refute this hypothesis.

The management of HUS secondary to STEC and \textit{S. dysenteriae} type 1 infections rests on supportive care, early renal replacement therapy and the use of blood components. Antibiotics are said to have only a limited role in STEC and may be potentially harmful (Wong et al., 2012). In contrast, HUS secondary to pneumococcal infection is aggressively managed by antibiotics (Copelovitch & Kaplan, 2008). Our patient was managed by broad-spectrum antibiotics and supportive therapy. Plasma exchange and infusions, the mainstay of treatment in atypical HUS secondary to complement factor deficiencies, are said to aggravate haemolysis in infections due to neuraminidase activity by providing more IgM anti-TFAg antibodies. They are hence contra-indicated in such cases (Copelovitch & Kaplan, 2008).

Even though our patient’s clinical presentation was highly suggestive of pseudomonal sepsis, which was later proven by blood culture, the possibility that \textit{Pseudomonas} was carrying the Shiga toxin gene cannot be completely ruled out. We did not look for this gene in the \textit{Pseudomonas} isolated, but the stool was negative for the \textit{stx} gene using PCR. An underlying complement defect triggered by pseudomonal sepsis is also possible, but this could not be investigated. A serum TFAg test would have added further evidence to the proposed role of neuraminidase in the pathogenesis of sepsis and HUS. A kidney biopsy was also not performed as it was not medically indicated. In spite of these limitations, it must be emphasized that many children, like our patient, may be mistakenly diagnosed with sepsis, and clinicians may fail to recognize the features of HUS. A detailed evaluation of such cases exhibiting the triad of HUS (thrombocytopenia, microangiopathy and acute kidney injury) may help to improve our understanding of this disorder.

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References


