

A 2-YEAR-OLD BOY WITH HEMOLYTIC UREMIC SYNDROME AND PNEUMOCEPHALUS

Sarah E. Martin, Steven D. Allen, Phillip Faught, Dean A. Hawley, Jose M. Bonnin, Eyas M. Hattab

Department of Pathology and Laboratory Medicine, Indiana University School of Medicine, Indianapolis, IN, USA

CLINICAL HISTORY

A previously healthy 2-year-old boy presented with one to two days of anuria and bloody diarrhea. He was admitted to the local children's hospital with a diagnosis of hemolytic uremic syndrome (HUS), presumably secondary to *E. coli* O157 but never confirmed. Laboratory studies revealed hemolysis, renal failure and thrombocytopenia. Eleven hours after admission, his blood oxygen saturations worsened and he was intubated. He was then noted to have fixed and dilated pupils. A head CT was performed, which revealed left frontal subcortical white matter vasogenic edema with left frontal gyral hyperdensity, as well as scattered pockets of pneumocephalus (Figure 1). Pneumocephalus without evidence of a calvarial fracture raised concern for an infectious process. Left-to-right midline shift with effacement of the cisterns and left uncal herniation were also observed. Neurosurgical consultation advised that no intervention was possible. The patient became bradycardic and required resuscitation, which unfortunately was not successful. He expired 14 hours after being admitted to the hospital. Antemortem bacterial blood cultures were positive.

PATHOLOGICAL FINDINGS

Gross pathologic examination of the brain revealed a large area of intraparenchymal hemorrhage with necrosis and cavitation over

the left frontal and parietal lobes. There was extensive midline shift with the left hemisphere being significantly larger than the right. Sequential coronal sections of the cerebrum displayed a $6.5 \times 6 \times 5.5$ cm area of dark brown discoloration with friable tissue and cavitation in the left frontal and parietal lobes, extending down the internal capsule to the midbrain (Figures 2 and 3). There was extensive vacuolization involving the cortex, white matter, basal ganglia, caudate and putamen, most severe in the right parietal lobe. Left uncal herniation was seen (Figure 4). Sequential transverse sections of the brainstem perpendicular to its long axis displayed an area of hemorrhage with cystic spaces and discoloration in the left midbrain, continuing into the left pons (Figure 5). Microscopic examination of the cortex, white matter, deep grey matter, hippocampi, cerebellum and brainstem revealed multiple holes of varying sizes (Figure 6), as well as diffuse colonization with rod-shaped bacteria, but without the expected tissue response (Figures 7–9).

General autopsy revealed a similar diffuse bacterial colonization of the lungs, kidneys, liver, and bowel (Figure 10), without an inflammatory response. The kidneys also showed stigmata of HUS, including numerous occlusive thrombi within the glomerular capillaries (Figure 11). There was also necrotizing colitis (Figure 10) and pneumatosis of the abdominal viscera including the colon, spleen, and retroperitoneal tissues.

What is the diagnosis?

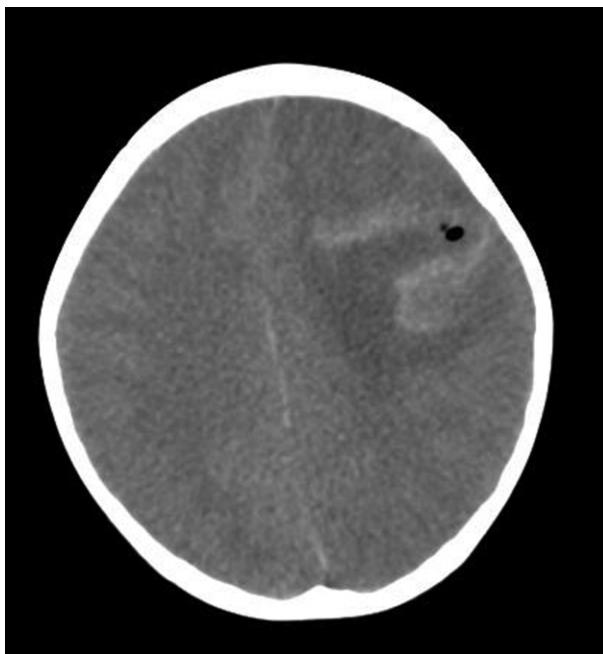


Figure 1.

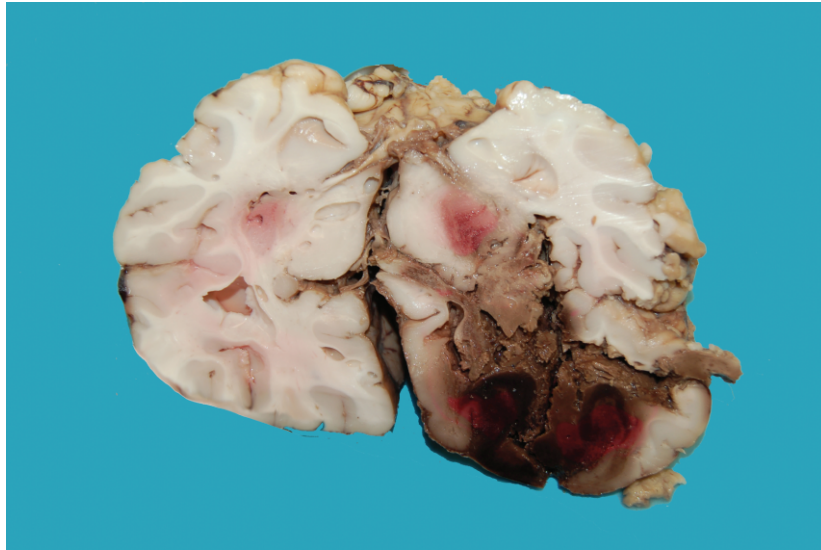


Figure 2.

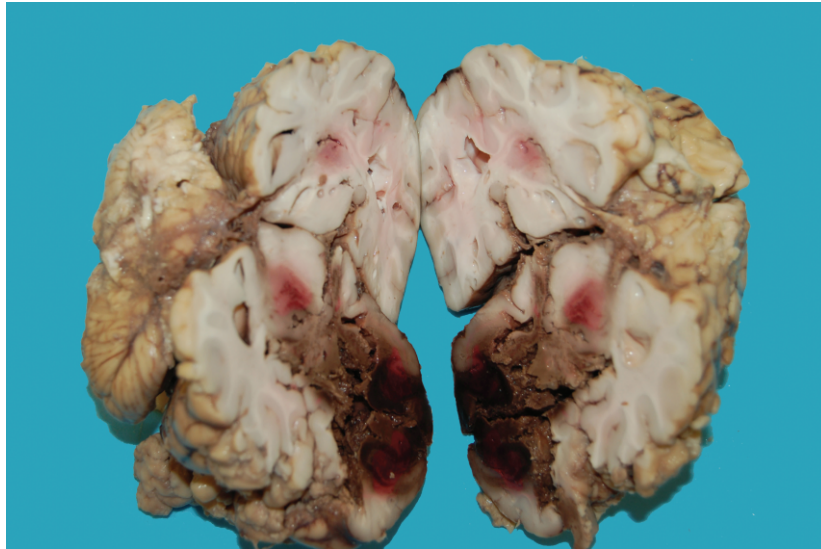


Figure 3.

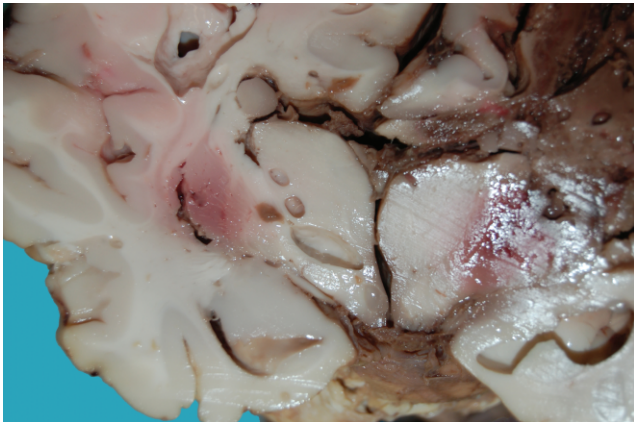


Figure 4.

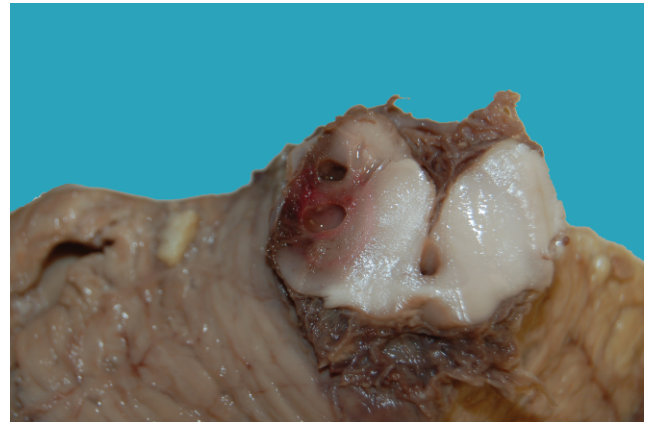


Figure 5.

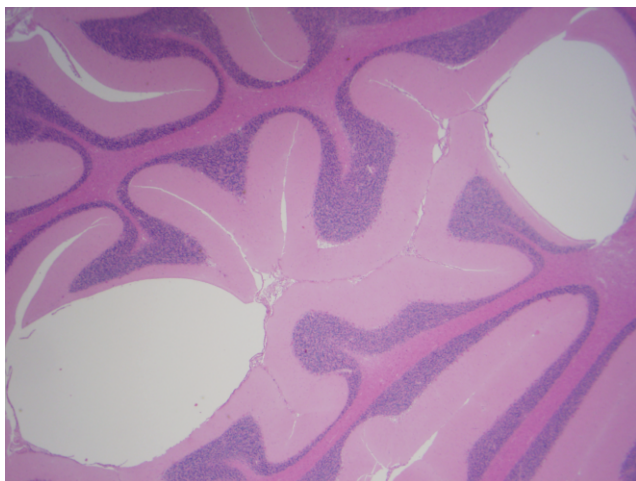


Figure 6.

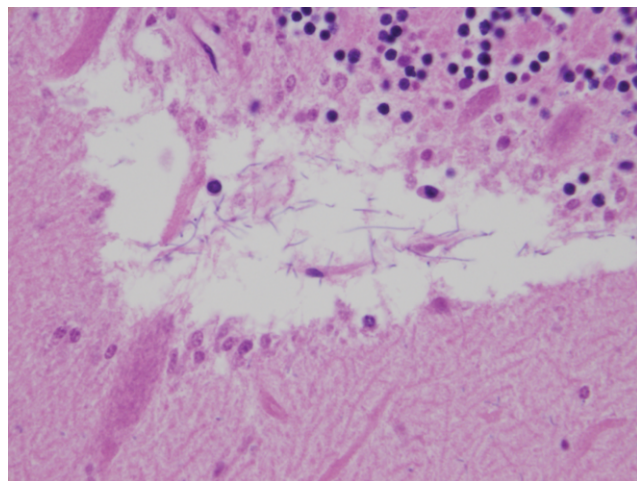


Figure 7.

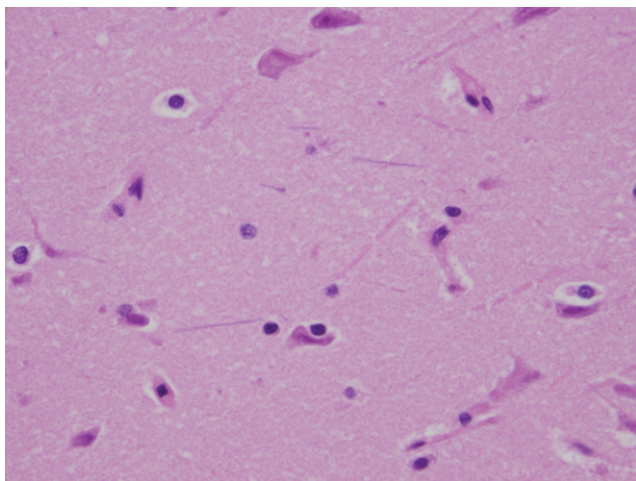


Figure 8.

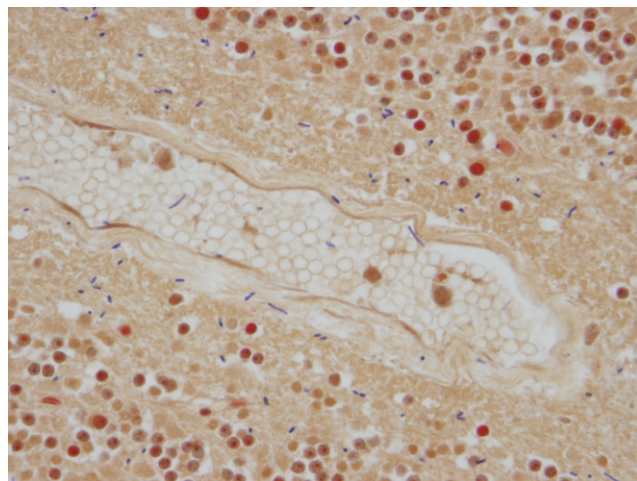


Figure 9.

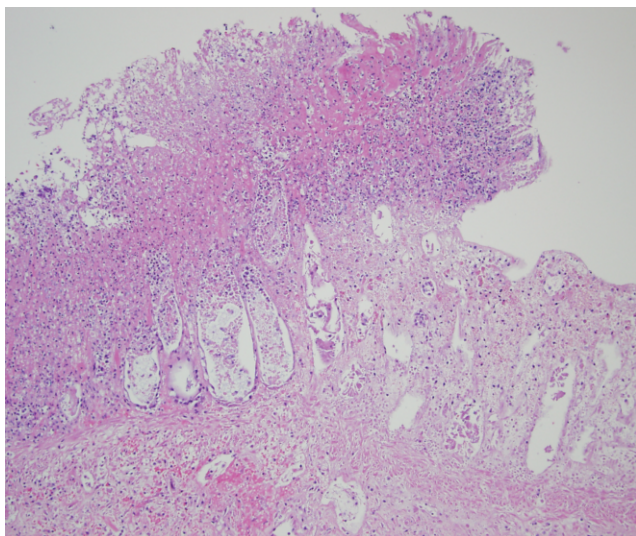


Figure 10.

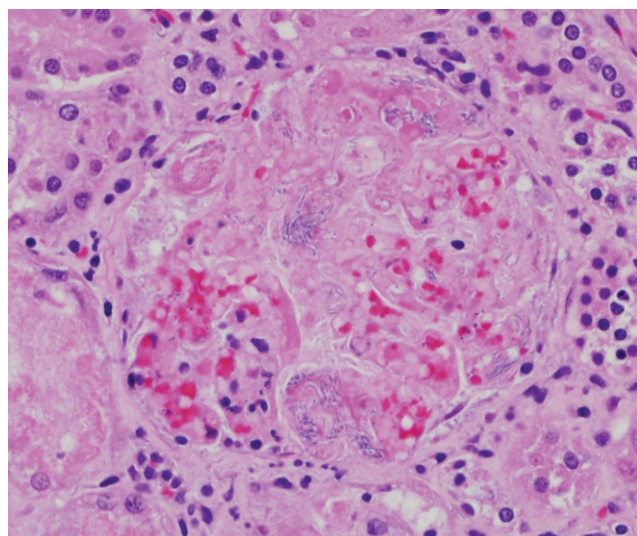


Figure 11.

DIAGNOSIS

Pneumocephalus due to *Clostridium septicum* in association with hemolytic uremic syndrome.

DISCUSSION

Clostridium septicum (*C. septicum*) is an anaerobic, spore-forming, gram-positive bacillus, first isolated by Pasteur and Joubert in 1877. It is found in soil and feces and is a well-known cause of gas gangrene in devitalized tissue (1, 2). *C. septicum* was reportedly responsible for much of the gas gangrene in wounded soldiers during World Wars I and II (1). Whether or not *C. septicum* is part of the normal human fecal flora is still debated. Studies have reported the presence of the organism in the feces of two to three percent of humans (1), and as many as 63 percent of people may carry the bacterium in the appendix (2).

There is a strong association between *C. septicum* bacteremia and malignancy, especially colon cancer and leukemia. These patients often have some devitalization of colonic tissue by the presence of tumor or necrosis of the tumor and hemorrhage as complications of therapy (3). *C. septicum* is an opportunistic pathogen, and this injured ischemic colonic epithelium is the likely portal of entry into the bloodstream. Children with hemolytic uremic syndrome may also develop bowel devitalization, either by direct injury to the bowel by infection with *E. coli* O157:H7 or devitalization of the bowel by thrombosis of small blood vessels secondary to the HUS (3). The mechanism of spread to distant sites appears to be hematogenous.

Sepsis, in this case from *C. septicum*, results in damage to the vascular walls in the vessels of the brain. These weakened vessels in combination with the patient's thrombocytopenia likely resulted in the large cerebral hemorrhage in this patient. *C. septicum* organisms were seen diffusely throughout the brain, but without the expected tissue response. There was, however, antemortem radiologic evidence of infection. Other organs with bacterial invasion also failed to show the expected tissue response. The patient was not known to be immunocompromised, so it is unknown as to why his tissues did not react as expected. Bacteria continue to disseminate during the agonal period, and because *C. septicum* is an anaerobic organism, it can continue to proliferate after death.

The multiple holes of variable sizes ("swiss-cheese" brain) seen in this patient are secondary to the gas-producing bacterium *C. septicum*, and are compatible with the patient's history of pneumocephalus. Several holes were seen radiologically pre-mortem, but the process continues after death.

C. septicum infection following HUS is a rare phenomenon, but several cases have been reported in the literature (1–4). In one report summarizing six cases (2), four had *C. septicum* involvement of the brain (brain abscess, pneumocephalus and meningoen-

cephalitis, cerebritis, and cerebritis and meningitis), one had myonecrosis, and one had sepsis and abdominal fasciitis. The mortality rate for *C. septicum* infections in children with HUS is high, with only two out of the six reported patients surviving. With brain involvement, the mortality rate is even higher at 75 percent, with the one known survivor having a brain abscess rather than diffuse pneumocephalus. Early identification of *C. septicum* infection in children with HUS is important because prompt antibiotic therapy may alter the course of this otherwise fatal illness (3).

REFERENCES

1. Barnham M, Weightman N (1998) Clostridium septicum infection and hemolytic uremic syndrome. *Emerg Infect Dis* 4(2):321–324.
2. Hunley TE, Spring MD, Peters TR, Weikert DR, Jabs K (2008) Clostridium septicum myonecrosis complicating diarrhea-associated hemolytic uremic syndrome. *Pediatr Nephrol* 23(7):1171–1175.
3. Riccio JA, Oberkircher OR (1988) Clostridium septicum sepsis and cerebritis: a rare complication of the hemolytic-uremic syndrome. *Pediatr Infect Dis J* 7(5):342–345.
4. Randall JM, Hall K, Coulthard MG (1993) Diffuse pneumocephalus due to Clostridium septicum cerebritis in haemolytic uraemic syndrome: CT demonstration. *Neuroradiology* 35(3):218–220.

Presented, in part, at the 86th annual meeting of the American Association of Neuropathologists, Philadelphia, Pennsylvania, June 10–13, 2009.

ABSTRACT

Clostridium septicum infection following hemolytic uremic syndrome is rare and carries a poor prognosis, especially when the brain is involved. We report a case of a previously healthy 2-year-old boy who presented with two days of anuria and bloody diarrhea. He was admitted to the local children's hospital with a diagnosis of hemolytic uremic syndrome, presumably secondary to *E. coli* O157. He soon required intubation and was noted to have fixed and dilated pupils. Head CT revealed left frontal subcortical white matter vasogenic edema and scattered pockets of pneumocephalus. The patient expired 14 hours after admission. Antemortem blood cultures grew *C. septicum*. Gross pathologic examination of the brain revealed a large intraparenchymal cerebral hemorrhage in the left frontal and parietal lobes. There was extensive cystic changes as well. Microscopic examination revealed vacuolization and diffuse colonization with rod-shaped bacteria, but without the expected tissue response. There have been only six previously reported cases of *C. septicum* infection following hemolytic uremic syndrome, four of which had brain involvement. Mortality rate is high, with the only known survivor among those with brain involvement having a brain abscess rather than diffuse pneumocephalus.