CASE IN POINT

Hemolytic Uremic Syndrome With Severe Neurologic Complications in an Adult

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The case of a female presenting with Shiga toxin-producing *Escherichia coli* and hemolytic uremic syndrome highlights a severe neurologic complication that can be associated with these conditions.

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Hemolytic uremic syndrome (HUS) is a rare illness that can be acquired through the consumption of food products contaminated with strains of Shiga toxin-producing *Escherichia coli* (*E coli*; STEC).[1] Between 6% and 15% of individuals infected with STEC develop HUS, with children affected more frequently than adults.[2,3] This strain of *E coli* releases Shiga toxin into the systemic circulation, which causes a thrombotic microangiopathy resulting in the characteristic HUS triad of symptoms: acute renal insufficiency, thrombocytopenia, and hemolytic anemia.[4-6]

Although neurologic features are common in HUS, they have not been extensively studied, particularly in adults. We report a case of STEC 0157:H7 subtype HUS in an adult with severe neurologic complications. This case highlights the neurological sequelae in an adult with typical STEC-HUS. The use of treatment modalities, such as plasmapheresis and eculizumab, and their use in adult typical STEC-HUS also is explored.

CASE

A 53-year-old white woman with no pertinent past medical history presented to the Bay Pines Veterans Affairs Healthcare System Emergency Department with a 2-day history of abdominal pain, vomiting, nausea, diarrhea, and bright bloody stools. She returned from a cruise to the Bahamas 3 days prior, where she ate local foods, including salads. She reported no fever, shortness of breath, chest pain, headache, and cognitive difficulties. She presented with a normal mental status and neurologic exam. Apart from leukocytosis and elevated glucose level, her laboratory results at initial presentation were normal, (Table). A stool sample showed occult blood with white blood cell counts (WBCs) but was negative for *Clostridium difficile*. She was started on ciprofloxacin 400 mg and metronidazole 500 mg on the day of admission.

Hematuria was found on hospital day 2. On hospital day 4, the patient exhibited word finding difficulties. Blood studies revealed anemia, thrombocytopenia, leukocytosis, and increasing blood urea nitrogen (BUN) and creatinine. A computed tomography scan of the head was normal. Laboratory analysis showed schistocytes in the peripheral blood smear.

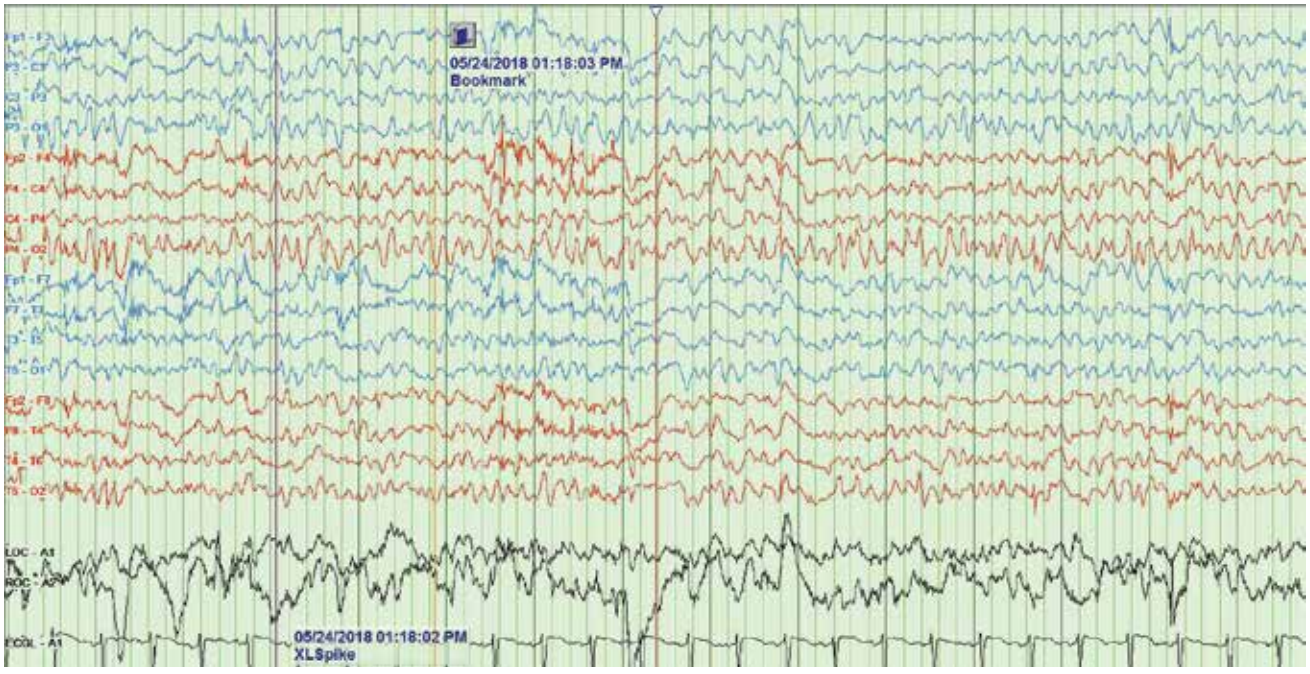
The patient's cognitive functioning deteriorated on hospital day 5. She was not oriented to time or place. Her laboratory results showed complement level C3 at 70 mg/dL (ref: 83-193 mg/dL) complement C4 at 12 mg/dL (ref: 15-57mg/dL). The patient exhibited oliguria and hyponatremia, as well as both metabolic and respiratory acidosis; dialysis was then initiated. Results from the stool sample that was collected on hospital day 1 were received and tested positive for Shiga toxin.

At this point, the patient's presentation of hemolytic anemia and thrombocytopenia in the setting of acute bloody diarrheal illness with known Shiga toxin, schistocytes on blood smear, and lack of pertinent medical history for other causes of this presentation made STEC-HUS the leading differential diagnosis. Plasmapheresis was ordered and performed on hospital day 6 and 7. Shiga toxin was no longer detected in the stool and antibiotics were stopped on hospital day 7.

The patient's progressive deterioration in mental status continued on hospital day 8. She was not oriented to time or place, unable to perform simple calculations, and could not spell the word "hand" backwards. Physicians observed

FIGURE 1

Electroencephalogram, Hospital Day 8



An electroencephalogram reveals an epileptic sharp wave at the right central parietal lobe.

repetitive jerking motions of the upper extremities that were worse on the left side. An electroencephalogram (EEG) revealed right hemispheric sharp waves that were thought to be epileptiform (Figure 1). The patient began taking levetiracetam 1500 mg IV with 750 mg bid maintenance for seizure control. Plasmapheresis was discontinued due to her continued neurologic deterioration on this therapy. Consequently, eculizumab 900 mg IV was given along with the *Neisseria meningitidis* (*N meningitidis*) vaccine and a 19-day course of azithromycin 250 mg po as prophylaxis for encapsulated bacteria.

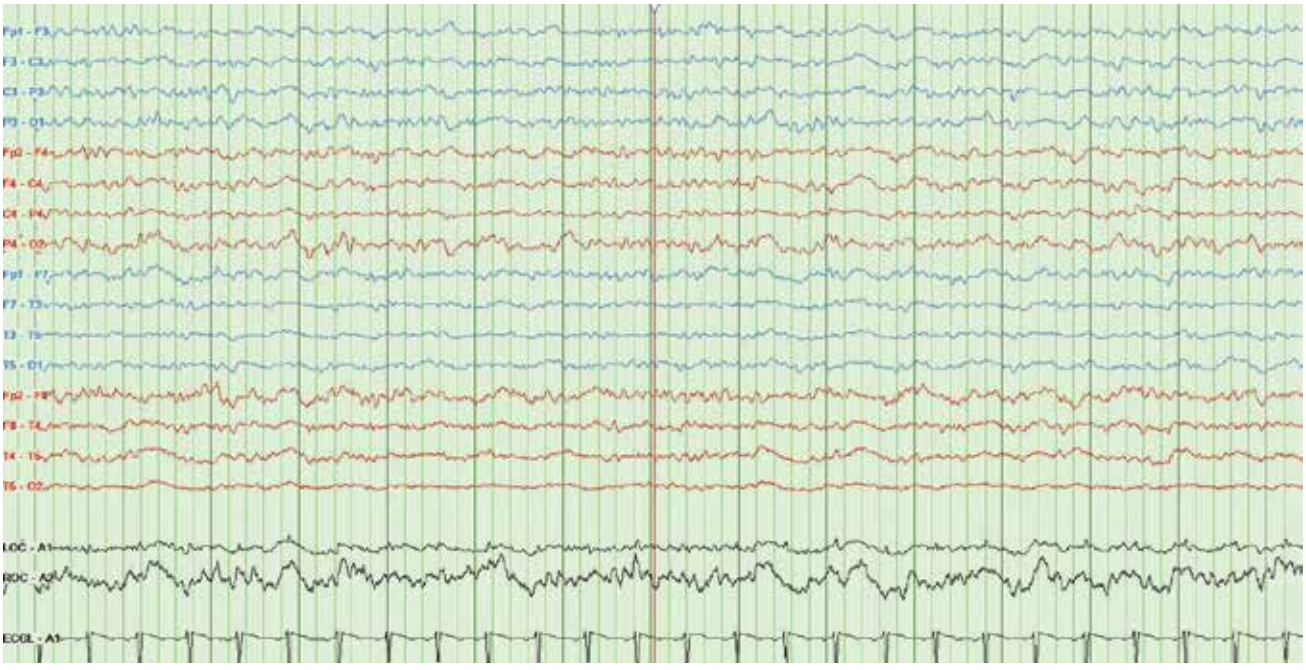
The patient continued to seize on hospital days 10 through 13. Oculocephalic maneuvers showed a tendency to keep her eyes deviated to the right. Her pupils continued to react to light. A repeat EEG showed diffuse slowing (5-6 Hz) with no epileptic activity seen (Figure 2). A second dose of eculizumab 900 mg IV was administered on hospital day 15. The patient experienced cardiac arrest on hospital day 16 and was successfully resuscitated. On hospital day 25 (10 days after receiving her second dose of eculizumab), the patient was able to speak and follow simple commands but exhibited difficulty concentrating and poor impulse control.

The patient was alert and oriented to person, place, time, and situation on hospital day 28 (6 days after the third and final dose of eculizumab). A neurologic exam was significant only for a slight intention tremor. She was continued on levetiracetam with a plan to be maintained on the medication for the next 6 months for seizure control. She was discharged on hospital day 30.

Twenty-eight days postdischarge (57 days postadmission), the patient showed marked recovery. She had returned to her previous employment as a business administrator on a part-time basis and exhibited no deficiencies in executive functioning or handling activities of daily living. Although she had been very active prior to this illness, she now experienced decreased physical and mental endurance; however, this gradually improved with physical therapy. She planned on returning to work on a full-time basis when she had regained her stamina. She also noticed difficulties in retaining short term memory since her discharge but believed that these symptoms were remitting. On examination her mental status and neurologic exam was significant for inability to continue serial 7s, left sided 4/5 muscle strength in quadriceps and thumb to 5th metacarpal adduction, bilateral 1+ reflexes

FIGURE 2

Electroencephalogram, Hospital Day 23



An electroencephalogram shows diffuse slowing (5-6 Hz) with no epileptic activity.

in muscle groups tested (triceps, biceps, brachioradialis, patellar, and Achilles), loss of dull pinprick sensation bilaterally at web of hands, deficit in tandem gait while looking away, and slight intention tremor on finger to nose testing bilaterally (with left hand tremor more pronounced than right). Her complete blood count was normal. Her recovery continues to be monitored in an outpatient setting.

DISCUSSION

HUS is characterized by 3 core clinical features: microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury.[4] Schistocytes are seen on peripheral blood smear and occur due to the passage of red blood cells over the microvascular thrombi induced by the disease. HUS can be classified as typical, atypical, or occurring with a coexisting disease. Typical HUS is associated with STEC 0157:H7 subtype, a bacterium known to be acquired through contaminated food and via human-to-human transmission.[6-8] In the case of typical STEC 0157:H7, the bacterium releases a verotoxin that damages the vascular endothelium, thereby leading to activation of the coagulation cascade and eventually the formation of thrombi.[4] It has been hypothesized that the Shiga toxin also activates the alternative complement pathway directly, which could contribute to thrombosis.[9] This would explain the findings of low complement levels in our patient. Atypical HUS is primarily attributable to mutations in the alternative complement pathway. Causes for the third type of HUS can include *Streptococcus pneumoniae,* HIV, drug toxicity, and alterations in the metabolism of cobalamin C.

Epidemiologically, 15.3% of children aged < 5 years develop typical HUS after exposure to STEC compared with 1.2% of adults aged 18 to 59 years. The median age of patients who developed HUS from STEC exposure was 4 years compared with 16 years for those who did not develop HUS.[2]

Neurologic manifestations increase mortality for HUS patients.[10] These have been described in the pediatric population as alteration in consciousness (85%), seizures (71%), pyramidal syndrome (52%), and extrapyramidal syndrome with hypertonia (42%).[11] Brain imaging in children has demonstrated hemorrhagic lesions involving the pons, basal ganglia, and occipital cortex.[11] Blood flow to areas such as the cerebellum, brainstem, and orbitofrontal area can be compromised.[10] Adult

TABLE

Evolution of Laboratory Data and Treatment

Variables	Hospital Day																
	1	5	6	7	8	9	10	11	15	16	18	19	22	24	29	30	63
Creatinine, mg/dL	0.59	4.02	4.21	3.98	5.31	4.16	5.21	4.12	4.5	3.93	4.2	5.11	2.29	2.8	1.69	1.53	
Urea nitrogen, mg/dL	11	39	41	40	54	38	54	43	52	57	55	84	33	41	16	14	
WBC, K/uL	19.1	15.0	12.5	11.5	15.2	17.7	14.0	19.6	18.1	30.9	9.8	7.8	8.6	11.7		7.0	7.0
Hgb, g/dL	14.1	8.7	7.0	7.6	7.3	8.8	9.2	5.5	9.1	9.0	6.6	8.7	8.6	9.2		8.7	11.2
Platelets, K/uL	188	21	24	15	29	17	20	33	237	465	242	216	179	146		172	189
Haptoglobin, mg/dL		< 30			< 30							121			84		
Sodium, mEq/L	137	125	131	138	136	138	135	135	137	138	137	138	139	140	140	141	
Potassium, mEq/L	4.1	3.9	3.9	3.6	3.4	3.7	4.1	4.2	5.2	4.5	4.3	4.7	3.4	3.7	3.4	3.7	
Glucose, mg/dL	117	116	101	124	132	135	179	193	116	210	122	134	130	111	198	156	
Calcium, mg/dL	8.1	7.3	7.3	7.6	8.1	7.5	7.6	7.5	8.3	8.4	7.9	7.8	7.9	8.5	9.4	9.1	
LDH, U/L		1395	1380	1601	2319	3327	3790	2207	548	509		380			240		150
Blood, pH		7.257					7.351	7.461			7.406	7.364		7.417			
PaCO2, mm Hg		39.8					54.4	43.7		45.9	38.6	35.6		36.0			
Troponin										0.13				0.34	0.08		
Transfusion type (units)		PLT (1)	RBC (2), FFP thaw	RBC (1), FFP thaw	RBC (2), PLT (1)	PLT (1)		RBC (3), FFP thaw (4)			RBC (2)						
Plasmapharesis			X	X													
Hemodialysis					X	X	X	X	X					X			
Ecolizumab IV, mg					900				900								

Abbreviations: AFR, apheresis; FFP, fresh frozen plasma; LDH, lactate dehydrogenase; PLT, platelets; RBC, red blood cells; WBC, white blood cells.

patients with HUS can present without lesions on cranial magnetic resonance imaging (MRI), but instead with transient symmetric vasogenic edema of the central brain stem.[12] Unfortunately in this case, MRI was not performed because it was thought to provide limited aid in diagnosis and to avoid unnecessary testing for the acutely ill patient.

The underlying pathophysiology of neurologic manifestations in patients may be due to a metabolic disturbance, toxin-mediated damage of the vascular endothelium, or toxin-induced

cytokine release resulting in death of neural cells and subsequent neuroinflammation. However, the most likely mechanism is parenchymal ischemic changes related to microangiopathy.[11,13] Pediatric patients often experience seizures and altered mental status, and their EEGs display delta waves.[13] This patient's diffuse slowing on her second EEG and altered mental status suggests that the neuropathologic mechanisms for typical HUS in adults may be similar to those in children.

HUS Treatment

The treatment and management of adults with typical STEC-HUS is evolving. The patient was first suspected to have an infectious colitis and empiric antibiotics were initiated. Some studies suggest that antibiotic administration may worsen the course of HUS in children as it may lead to release and subsequent absorption of Shiga toxin in the intestine.[9,14] However, there is little evidence to suggest harm or efficacy of administration in adults. It is unclear what role antibiotic administration played in the recovery time of HUS given the co-administration of other treatments such as eculizumab and plasmapheresis, but it does appear to have helped with the initial *E coli* infection.

Plasmapheresis was subsequently administered, due to its documented benefit in the treatment of HUS.[15] However, it should be noted that even though plasmapheresis is currently used in patients with CNS involvement, it remains unproven with conflicting information on its efficacy.[3,16] The mechanism of action is unclear, but it has been hypothesized that plasmapheresis prevents microangiopathy caused by microthrombi.[3,16] For this reason, eculizumab is becoming the mainstay for treatment of STEC-HUS with neurologic complications given the lack of well researched alternative treatments. In this case study, the use of plasmapheresis did not result in clinical improvement, and was abandoned after 2 days of treatment.

Eculizumab is a humanized, recombinant monoclonal IgG antibody that is a terminal complement inhibitor of the alternative complement system at the final step to cleave C5.[17] The Shiga toxin may directly activate the complement system via the alternative pathway, which can result in uncontrolled platelet and white blood cell activation and depletion, endothelial cell damage, and hemolysis. The galvanized complement system leads to a series of cascading events that contribute to organ damage and death.[9] Eculizumab is FDA approved for use in atypical HUS.[18] It also can be used off-label to treat typical-HUS in adults with neurologic complications.

Eculizumab interferes with the immune response against encapsulated bacteria because it inhibits the alternative complement pathway. Thus, vaccination against *N meningitides* is recommended 2 weeks prior to the administration of eculizumab. However, in situations where the risks of delaying eculizumab for 2 weeks are greater than the risk of developing an *N meningitides* infection, eculizumab may be given without delay.[18] Given the rapid deterioration of our patient's condition, the vaccine and eculizumab were given together with prophylactic azithromycin. Although penicillin is the standard for prophylaxis in this situation, the patient's penicillin allergy led to the use of azithromycin 250 mg po once a day. Literature also suggests azithromycin reduces the carriage duration of *E coli*-induced colitis.[19] As such, it is possible that some improvement in the patient's condition could be attributed to the elimination of the pathogen and toxin.

CONCLUSION

Three doses of eculizumab were administered at weekly intervals, with the first dose on hospital day 8 and the final dose on hospital day 22. Prior to the first dose, the patient displayed significant decline in mental status with EEG findings of right hemisphere epileptogenic discharges. After her third dose, she was found to have a drastically improved mental status exam and a normal EEG. One week later, she was discharged home. At the time of her 1-month follow-up, she was independent in all activities of daily living and had returned to part-time work. Apart from subtle cognitive changes, the remainder of her neurologic exam was normal.

There is evidence that supports the efficacy of eculizumab in children with HUS with neurologic symptoms on dialysis.[20] However, its use in adults is not well established.[21] This patient required dialysis and had neurologic symptoms similar to pediatric patients described in the literature, and responded similarly to the eculizumab. The rationale for the use of eculizumab in STEC-HUS also is

evidenced by in vitro demonstrations of complement activation in STEC-HUS.[22-25] This case report adds to the literature supporting the use of eculizumab in adult patients with typical HUS with neurological complications. Further research is necessary to develop guidelines in the treatment of adult STEC-HUS with regards to neurologic complications.

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