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BRIEF REPORT

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Hemorrhagic colitis due to a novel *Escherichia coli* serotype (O121:H19) in a transplant patient

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Abstract Infection due to enterohemorrhagic *Escherichia coli* (EHEC) has not been described in immunosuppressed patients. We recently saw a case of EHEC infection caused by a novel Shiga toxin II-producing *Escherichia coli* serotype (O121:H19) that caused hemorrhagic colitis in a patient with renal and cardiac transplants. The patient's signs, symptoms, and colon pathology were similar to reports of EHEC infection in immunocompetent patients. This case suggests that the immunosuppressed state may not alter the clinical presentation or histopathologic findings of this disorder. Assays for EHEC are not routinely done at most hospitals. Therefore, clinicians caring for transplant patients should be aware of the typical clinical presentation of EHEC infection, so that they can initiate appropriate laboratory investigation in suspected cases.

Keywords Enterohemorrhagic *Escherichia coli* (EHEC) · Kidney transplantation · Heart transplantation · Colitis · Hemolytic-uremic syndrome

Abbreviations *CMV* Cytomegalovirus · *EHEC* Enterohemorrhagic Escherichia coli · *HUS* Hemolytic-uremic syndrome · *SMAC* Sorbitol MacConkey agar

Introduction

In the last two decades, enterohemorrhagic *Escherichia coli* (EHEC) has emerged as an important and widely publicized cause of gastrointestinal disease in humans. The clinical characteristics of EHEC infection have been well documented in immunocompetent hosts, but little is known about the clinical presentation of this disease in immunocompromised hosts [2, 5]. We recently saw a patient with a functioning heart transplant, and two prior renal transplants that had failed, who developed EHEC infection with a novel *E. coli* serotype. We report on the course of his disease and histopathological findings.

EHEC infection can cause either bloody or nonbloody diarrhea. In outbreaks, from 35% to 90% of cases have had blood in their stools [2, 3]. Hemolytic-uremic syndrome (HUS) or thrombotic thrombocytopenic purpura occur in about 6% of clinical cases, and the disease is fatal in 1% of affected individuals [6]. The pathogenicity of EHEC appears to be due to the production of two cytotoxins by *E. coli* [4]. These toxins are collectively referred to as Shiga toxins I and II due to the close resemblance to the toxin produced by *Shigella dysenteriae* type 1 [6]. More than 100 *E. coli* serotypes producing Shiga toxins have been isolated from humans; however, most gastrointestinal disease has been associated with O157:H7 [3, 4].

Most outbreaks of EHEC have been linked to the consumption of undercooked beef, raw milk, or other products contaminated by the intestinal contents of cattle [8]. Serotype O157:H7 has caused over sixty documented outbreaks of foodborne illness in communities, schools, nursing homes and day care facilities in the United States [5]. With enhanced detection and surveillance techniques, an increasing number of *E. coli* that are not O157 serotypes are being identified as EHECs.

Case report

A 53-year-old man was admitted to the hospital because of nausea, vomiting, crampy abdominal pain, bloody diarrhea, and dehydration. The patient had renal failure due to Alport's syndrome. He was undergoing hemodialysis after twice having received cadaveric renal transplants (in 1984 and 1993) that had failed. A cardiac transplantation was performed in 1989 for ischemic cardiomyopathy. He also suffered from recurrent pancreatitis, steroid-induced diabetes, peripheral neuropathy, and hepatitis C infection and had undergone repair of an abdominal aneurysm in the past.

Two weeks earlier, the patient had been admitted to the hospital for acute heart failure. An echocardiogram revealed a decrease in ejection fraction, but an endomyocardial biopsy did not reveal rejection. The patient responded to medical therapy and was discharged 10 days later. At the time of discharge the patient had several loose stools. During the next 48 hours the patient's diarrhea worsened and became grossly bloody, and he developed crampy, nonlocalized abdominal pain and nausea. Over the subsequent 24 hours he developed vomiting, progressive weakness, and dehydration, and he was readmitted to the hospital.

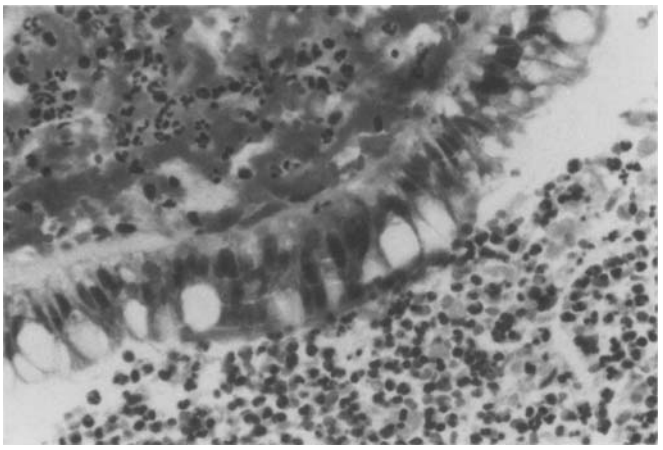

Fig. 1 Acute colitis with acute hemorrhage, neutrophilic infiltrate of lamina propria and an overlying pseudomembrane composed of neutrophils, fibrin, and red blood cells (H&E, × 310)

The patient's medications included cyclosporine, prednisone, fluoxetine, gabapentin, allopurinol, insulin, ranitidine, and aspirin. The patient lived in eastern Tennessee with his wife, who was asymptomatic. He drank only city or bottled water and denied eating undercooked food. There was no family history of inflammatory bowel disease. The patient denied fever, hematemesis, previous gastrointestinal bleeding, and back or chest pain.

Vital signs were: temperature, 37 °C; pulse, 130; respirations, 26; and blood pressure, 115/72 mmHg. The patient appeared ill and was lethargic and pale. Bibasilar crackles were heard in the chest, and the cardiac examination revealed sinus tachycardia, without murmurs or gallops. The abdomen was soft, but diffusely tender to palpation, with hypoactive bowel sounds. Multiple surgical scars were noted, but there was no evidence of abdominal masses, organomegaly, guarding, rebound, or flank tenderness. Rectal exam was normal except for the presence of guaiac-positive stool.

The white blood cell count was 20.7 × 10^9/l and the hematocrit was 48%. Electrolytes were normal; glucose, 11.4 mmol/l; blood urea nitrogen, 7.1 mmol/l; and serum creatinine, 71.6 mmol/l. Liver and pancreatic enzymes were normal except for a total bilirubin level of 35.9 mg/dl. A chest radiograph revealed a small, left-sided pleural effusion. An abdominal radiograph showed a nonspecific bowel gas pattern and calcified abdominal vessels. Abdominal CT scan exhibited marked bowel wall thickening involving the ascending, transverse, and descending colon with pericolic stranding. There was no evidence of sigmoid involvement. The initial diagnosis was infectious colitis. The patient was given intravenous fluid and started on oral metronidazole and levofloxacin and intravenous ganciclovir.

Over the next 3 days the patient's diarrhea decreased and he had no further vomiting. Colonoscopy revealed severe colitis from the cecum to the proximal transverse colon and mild inflammation involving the distal transverse and descending colon. The sigmoid colon and rectum appeared normal. Biopsies from the colon revealed acute colitis with a striking neutrophilic infiltrate of the lamina propria accompanied by edema, acute hemorrhage, fibrin deposition, and focal overlying pseudomembrane formation (Fig. 1). No viral inclusions or areas of bacterial overgrowth were noted. Other areas of large bowel demonstrated a pattern suggesting ischemic colitis with extensive ulceration and loss of superficial

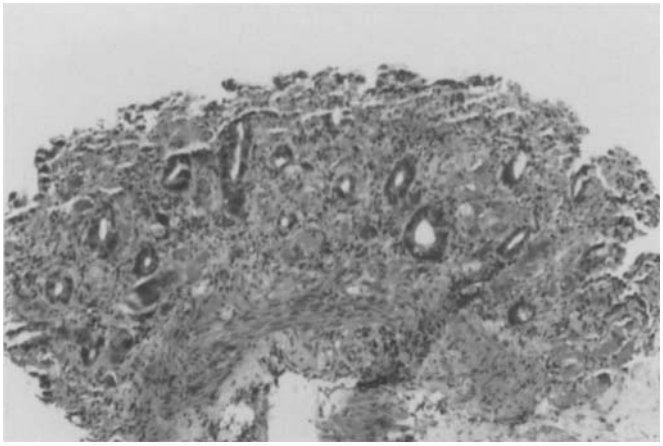

Fig. 2 Large bowel demonstrating ischemic pattern of injury with total loss of superficial glands, inflammation of lamina propria, and preservation of crypt epithelium (H&E, × 70)

colonic glands while basilar crypt epithelium remained intact (Fig. 2). Biopsies from the rectosigmoid revealed only focal, mild, acute colitis. Admission blood and urine cultures, stool for *Clostridium difficile* toxin by enzyme immunoassay, and tests for ova and parasites were negative. Stool cultures plated on sorbitol MacConkey agar (SMAC) did not reveal any sorbitol-negative colonies, characterisitic of *E. coli* O157:H7. However, due to the clinical suspicion of enterohemorrhagic *E. coli*, multiple, sorbitol-positive *E. coli* colonies were isolated and forwarded to the Centers for Disease Control and Prevention laboratory for further analysis. On the fifth day in hospital, the patient's white cell count had decreased to 11.3×10^9/l, and all his symptoms had resolved. Blood antigenemia for cytomegalovirus (CMV) was negative, and no CMV inclusion bodies were seen on mucosal biopsies. Ganciclovir was discontinued. The patient continued to improve daily and was discharged after 8 days. He had been afebrile throughout his hospital stay. The patient received a total course of 14 days of oral levofloxacin and metronidazole. The patient's stool culture revealed an *E. coli* O121:H19, which was positive for Shiga toxin type II by polymerase chain reaction analysis performed by the Centers for Disease Control and Prevention laboratory.

Discussion

To our knowledge, this is the first report of illness due to enterohemmorhagic *E. coli* in a transplant recipient. Neither have EHEC infections been described in patients with severe neutropenia or HIV infection. It is not known whether defects in the immune system alter the frequency or clinical presentation of EHEC infection. Infection with EHEC does not appear to provide uniform protection against reinfection since recurrent EHEC infection and recurrent HUS due to EHEC have occurred in individuals with normal immunity [9, 10]. Yet the higher incidence of symptomatic EHEC infection in young children and elderly persons has been offered as evidence for a role of the immune system in controlling the disease [8]. Our patient was significantly immunosuppressed by his antirejection therapy and chronic renal failure, but nevertheless had a very typical presentation of EHEC infection. This suggests that the clinical course of EHEC infection may not be altered by the immunosuppressed state.

The clinical signs and symptoms of *E. coli* O157:H7 infection are well documented [5, 11]. Most patients with *E. coli* O157:H7 infection have abdominal cramps and tenderness, but fever is usually absent, and when present, is often low-grade [4, 8]. Both bloody diarrhea and abdominal tenderness were major components of our patient's clinical presentation. In addition, our patient remained afebrile throughout his course. Non-O157 EHECs have been isolated from both bloody and nonbloody diarrhea. As a group, however, they appear less likely to cause bloody diarrhea than *E. coli* O157:H7 [12, 13]. Our patient's isolate, *E. coli* O121:H19, has been shown to produce Shiga toxin, but the number of clinical isolates is limited and the clinical presentation not well characterized in the literature [4].

Previous investigators have noted the predominance of right-sided colonic findings in patients with *E. coli* O157:H7 infection [14]. Our patient's abdominal CT scan and endoscopic biopsy samples revealed evidence of pancolitis, but during endoscopy the bowel showed far greater involvement of the ascending and early transverse colon. Only focal, mild colitis was seen on the biopsy of the rectosigmoid in contrast to the well-developed ulcerations and pseudomembrane formation noted on more proximal biopsies. The usual histologic findings of patients with *E. coli* O157:H7-associated colitis resemble a combination of ischemic and infectious patterns of injury and are similar to the changes described in *Clostridium difficile*-associated colitis [15]. Because *C. difficile* infections are common in transplant patients, some EHEC infections might be attributed to "toxin-negative" *C. difficile* infection.

Our patient did not develop HUS. It is not known whether immunosuppression enhances or decreases one's risk of developing HUS in the course of EHEC infection. The proportion of patients developing HUS in reported outbreaks of EHEC varies from 0% to 16% [8]. Shiga toxin-producing *E. coli* that do not have the O157:H7 serotype are less frequently reported than *E. coli* O157:H7 in most series of HUS [5]. For example, one study of patients with HUS revealed EHEC isolates in 82%, but only 7% were non-O157 serotypes [16]. In part, this could be due to the greater difficulty of detecting non-O157 isolates.

The diagnosis of EHEC infection requires a high level of suspicion. SMAC agar is the medium of choice for screening stool samples in suspected EHEC cases [17]. Sorbitol-negative (clear) colonies should be selected from the SMAC plate and tested with available *E. coli* O157 antiserum [15]. Sorbitol-positive Shiga toxin-producing *E. coli* O157:H7 and non-O157 isolates are less

common in EHEC patients; however, in patients or which there is a high clinical suspicion, as in the case of our patient, it may be useful to screen these colonies of *E. coli* for toxin production.

There is no specific therapy that has been proved to benefit patients with gastrointestinal disease caused by EHEC, although Synsorb, an orally administered cellular receptor for Shiga toxin, is now being evaluated in clinical trials [1]. Although the majority of EHEC serotypes are susceptible to antimicrobial agents, limited retrospective studies have shown little impact of antimicrobial use on outcome [6]. There is concern that antibiotic use may actually be detrimental since some antibiotics, such as sulfonamides and quinolones, increase Shiga toxin production in vitro [7, 18]. Our patient's apparent response to antimicrobial therapy may simply reflect the natural history of the disease.

Clinicians caring for immunosuppressed patients should be aware that these patients can develop hemorrhagic colitis from EHEC, including non-O157 serotypes. This case suggests that the immunosuppressed state does not alter the clinical presentation or histopathologic findings of this disorder. Since assays for EHEC are not routinely done at most hospitals, diagnosis requires a high index of suspicion and close communication with the microbiology laboratory.

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