CASE REPORT

Severe gastrointestinal cryptosporidiosis three years after multi-visceral transplantation

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Abstract

Background: Cryptosporidia are known to cause opportunistic gastrointestinal tract infections with variable severity. Such infections can be life-threatening in transplant recipients. We report the evolution of cryptosporidiosis in a multi-visceral transplant recipient with repeated endoscopic biopsies until specific therapy was instituted.

Case description: A 40-year-old woman with a history of multi-visceral (stomach, duodenum, small bowel, liver, and pancreas) transplantation presented with severe acute diarrhea three years after transplantation. Endoscopic biopsies of the stomach, duodenum, and lower small bowel were performed and submitted for histologic examination to assess the possibility of rejection. Microscopic examination of the lower small bowel biopsy specimens revealed mild to moderate inflammation and the presence of microorganisms with features of Cryptosporidia in the intestinal crypts. No evidence of rejection was found. While waiting for the availability of nitazoxanide, the patient was initiated on metronidazole, but her diarrhea worsened. Eleven days later, new biopsies were obtained, revealing abundant Cryptosporidia in the lower small bowel and duodenal specimens and few Cryptosporidia in the gastric biopsy specimen. Nitazoxanide was soon administered, leading to clinical improvement. Six weeks later, new biopsies showed complete resolution of inflammation and the absence of microorganisms.

Conclusion: Histological examination of biopsy specimens is crucial for the diagnosis of cryptosporidiosis, which can threaten the life of immunocompromised individuals. The importance of specific antiprotozoal treatment must be emphasized. HIPPOKRATIA 2022, 26 (3):121-123.

Keywords: *Cryptosporidium*, multi-visceral transplantation, severe opportunistic infection

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Introduction

Cryptosporidiosis is a parasitic disease infecting humans through the fecal-oral route and causing acute diarrhea[1]. While immunocompetent individuals usually clear the infection without specific treatment, this protozoon may cause severe, life-threatening disease in immunocompromised patients[2]. In patients with small bowel transplants, acute onset diarrhea is often the presenting symptom of acute rejection. The gold standard to reach a definite diagnosis of rejection versus opportunistic infection is the histologic examination of biopsy specimens, aided by other laboratory tests[3]. We present the case of a multi-visceral transplant recipient with acute diarrhea and a challenging clinical course due to the lack of immediately available specific treatment, illustrating the importance of histologic examination for diagnosis. Examination of repeated gastrointestinal biopsy specimens revealed the dissemination of Cryptosporidia over time from the lower small bowel to the duodenum and stomach.

Case Description

A 40-year-old woman with a history of multi-visceral transplantation presented with acute severe watery diarrhea of more than 10 bowel movements per day. Three years earlier, the patient had undergone stomach, duodenum, small bowel, liver, and pancreas transplantation due to mesenteric ischemia and acute liver failure due to long-term total parenteral nutrition support. Since then, multiple surveillance biopsies for transplant rejection had been negative. In the current presentation, the patient was on tacrolimus 4 mg/d and mycophenolate mofetil 1 gr/d. Biopsies of the stomach, duodenum, and lower small bowel were performed and submitted for histologic examination. There was mild to moderate inflammation in the small bowel biopsy specimen on microscopic examination. The inflammatory infiltrate comprised neutrophils, lymphocytes, eosinophils, and plasma cells. On high-power examination, a moderate number of microorganisms with features of Cryptosporidia were identified in the small bowel crypts (Figure 1A); their presence

was confirmed on Giemsa stain (Figure 1B) and periodic acid-Schiff (PAS) stain (not shown). No evidence of rejection was found.

Intravenous rehydration treatment was promptly initiated. The patient was also started on metronidazole 500 mg three times a day. The immunosuppression regimen was reduced, including a temporary interruption of mycophenolate mofetil and a reduction in tacrolimus dosage. At the same time, an effort to obtain nitazoxanide was initiated; however, there was a delay in the delivery of this drug, and diarrhea worsened. New biopsies were taken 11 days later, revealing abundant Cryptosporidia in the lower small bowel. In addition, a moderate number of these microorganisms was present in the duodenum, accompanied by moderate inflammation (Figure 2A). A few Cryptosporidia were also identified in the gastric biopsy specimens, accompanied by mild inflammation (Figure 2B). No evidence of rejection was found.

Soon afterwards, the patient was administered nitazoxanide 1 g twice daily. The diarrhea resolved after seven days of treatment. New biopsies taken six weeks later showed complete resolution of the inflammation. No microorganisms or evidence of rejection were present.

The patient is alive and well two years after her cryptosporidiosis presentation.

Discussion

Cryptosporidiosis can involve any segment of the gastrointestinal system, the most common site being the upper small bowel[4]. Other sites include the large bowel, the biliary tract, and the stomach. Pulmonary infection has also been reported[1,4]. *Cryptosporidium parvum* and *Cryptosporidium hominis* are members of the Apicomplexa phylum infecting humans[4]. *Cryptosporidium* infects humans through the ingestion of oocysts in contaminated food and water. The parasite is found in surface water samples and is resistant to chlorine. When oocysts enter the intestinal epithelial cells, they develop into infectious forms[4]. The parasites assume an extracytoplasmic, intracellular location.

Cryptosporidia can be detected by examination of stool and cytology specimens. The oocysts measure 4-6 μm in diameter and are known to stain with a modified acid-fast procedure. On acid-fast staining, the parasites are bright red against a blue-green fecal debris background[3]. Size measurement is of importance to differentiate *Cryptosporidium* oocysts from those of *Cyclospora cayetanensis*, which are similar in appearance and acid-fast, but larger. Methods based on antigen detection improve Cryptosporidia identification yield in these specimens[3].

In histologic sections, the parasites can be detected on

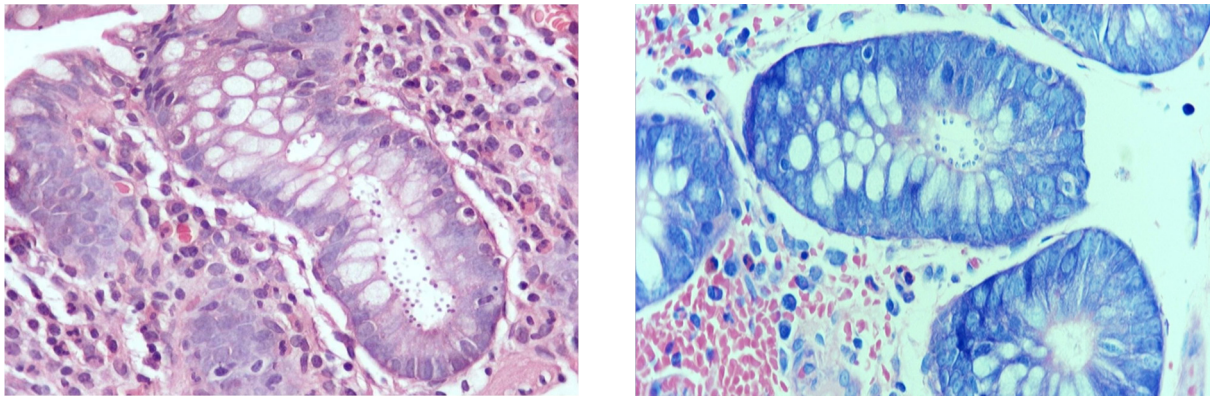

Figure 1: Histology images of the biopsy specimen of the small intestinal allograft with moderate inflammation and *Cryptosporidium* oocysts along the lumen of a crypt (A: hematoxylin-eosin stain, x 400; B: Giemsa stain, x 400).

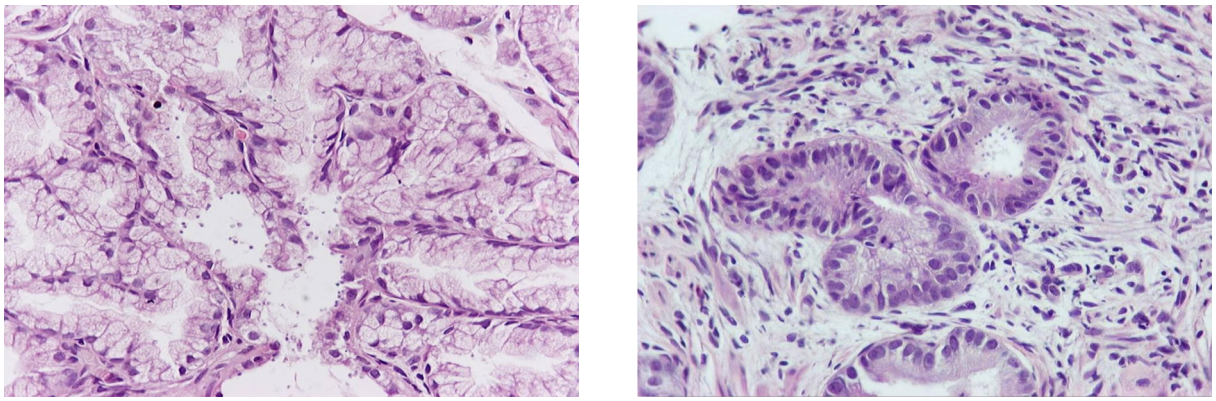

Figure 2: Histology images of biopsy specimens of duodenal (A) and gastric (B) allografts with *Cryptosporidium* oocysts in Brunner's glands and a gastric gland (A and B: hematoxylin-eosin stain, x 400).

high-power examination of hematoxylin-eosin-stained material (Figure 1A, Figure 2A, Figure 2B); their presence can be further confirmed with Giemsa (Figure 1B) and PAS stains. Cryptosporidia are recognized as small, basophilic, spherical bodies on the luminal (apical) surface of the epithelial cells or in the crypts, providing a "bluebead" appearance. Mucosal inflammatory cell infiltration with crypt abscesses and crypt hyperplasia is common. Cryptosporidia increase epithelial cell apoptosis. In our case, Cryptosporidia were detected in the lower small intestinal allograft at the beginning of the disease course. Eleven days later, the microorganisms were also found in the duodenal and gastric allografts.

Cryptosporidiosis is a common cause of refractory diarrhea among solid organ transplant (SOT) recipients[5]. Most reports include single cases or small case series and involve kidney[5-8], liver[6,9], pancreas[6], and heart[6] transplant recipients. The incidence of cryptosporidiosis among SOT recipients ranges from 0.34 % to 28.5 %[5]; the highest incidence has been reported in India[8]. Environmental risk factors include travel to endemic countries, contact with farm animals, and exposure to recreational water[10]. In a study involving 47 SOT recipients with cryptosporidiosis, Lanternier et al[6] noted that the infection occurred at a median time of 3.4 years posttransplant, while the median time between the first symptoms and the diagnosis was ten days.

Most immunocompetent individuals will recover from Cryptosporidia infection without treatment. Diarrhea can be managed by fluid and electrolyte replacement, while anti-diarrheal medicines may help slow down the symptoms. The only Food and Drug Administration (FDA)-approved drug for treating cryptosporidiosis in immunocompromised individuals is nitazoxanide. Its mechanism of action, including one of its metabolites, has been investigated *in vitro* and is thought to interfere with the essential for anaerobic energy metabolism pyruvate:ferredoxin oxidoreductase (PFOR) enzyme-dependent transfer reaction. In three randomized controlled trials, nitazoxanide has been found effective in treating cryptosporidiosis in children and adult immunocompetent patients[11-13]. Trials in immunocompromised patients have shown variable results, with better outcomes in non-HIV than HIV-infected patients[10]. Combinations of antiparasitic medications may often be needed in immunocompromised patients[7,8].

In conclusion, this case illustrates that cryptosporidiosis can mimic acute rejection in patients with intestinal allografts and can cause severe, life-threatening diarrhea. Histologic examination of biopsy specimens provides a rapid and efficient method of diagnosis. Nitazoxanide treatment is often effective and should be readily available for early treatment.

Conflict of interest

Authors declare no conflicts of interest.

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