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Cryptosporidiosis in a transplant recipient with severe intractable diarrhea: Detection of *Cryptosporidium* oocysts by intestinal biopsies

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Abstract

Disseminated *Cryptosporidium* infection results in manifestations similar to those of graft-versus-host disease (GVHD), which hampers the detection of *Cryptosporidium* infection after allogeneic hematopoietic stem cell transplantation. Surveillance of oocysts on the surface of intestinal epithelial cells is needed for early and appropriate detection of *Cryptosporidium* infection in transplant recipients on immunosuppressants with severe intractable diarrhea. We present the first case of *Cryptosporidium meleagridis* infection in Japan after allogeneic cord blood transplantation.

KEYWORDS

cord blood transplantation, Cryptosporidiosis, *Cryptosporidium meleagridis*, graft-versus-host disease, T-cell lymphoblastic lymphoma

1 | CASE REPORT

A 63-year-old female in second complete remission from T-cell lymphoblastic lymphoma was referred to our hospital for umbilical cord blood transplantation. She was treated with a non-myeloablative conditioning regimen consisting of intravenous infusion (iv) of 30 mg/m^2 fludarabine for 6 days and 40 mg/m^2 melphalan for 2 days, followed by 2 Gy total body irradiation for 2 days. A continuous iv of tacrolimus (Tac) and 2000 mg/day oral mycophenolate mofetil (MMF) were initiated as GVHD prophylaxis. On day 18 after transplantation, her neutrophil count recovered, and she developed a mild skin eruption and watery diarrhea of >1000 mL/day. No bacterial, mycotic, or *Clostridium difficile* toxin A were detected in the stools. On day 20, we performed a colonoscopy, which indicated mild colitis. The biopsy of the edematous lesions revealed epithelial apoptosis with infiltration of inflammatory cells, which is consistent with acute gut GVHD. There were no findings of cytomegalovirus colitis. Based on the diagnosis of acute GVHD, 1 mg/kg/day prednisolone (PSL) was initiated in addition to Tac and MMF. Because her diarrhea worsened, 250 mg/day methylprednisolone for 3 days was added to her regimen. However, the watery diarrhea still persisted. Intestinal biopsies were repeated on day 39, based on which acute GVHD was again diagnosed. We then treated the patient with 0.5 mg/kg/day anti-thymocyte globulin on days 47, 49, and 62. Despite these treatments, her diarrhea became worse similar to that which occurs in cholera, and she developed vomiting with increased plasma levels of bilirubin. The laboratory data on day 82 were as follows: total bilirubin 3.6 mg/dL, aspartate aminotransferase 109 U/L, alanine aminotransferase 127 U/L, and γ-glutamyl transpeptidase 563 U/L.

1.1 | Diagnosis and treatment

The colonoscopy on day 82 indicated mild colitis with mucosal erosion, which we observed on day 20, and edema of the Bauhin valve

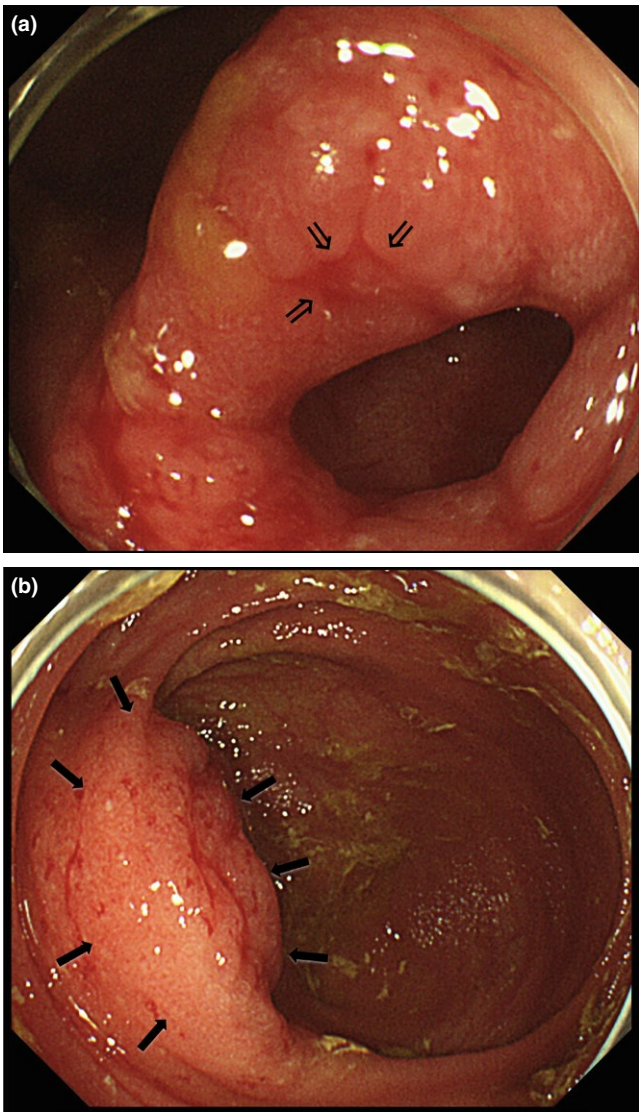

FIGURE 1 (a, b) Endoscopic appearances of the large intestine and Bauhin valve. A colonoscopy was performed on day 82. Mild erosion was widely observed on the mucosa in the colon. (a) The fold of the ascending colon. A small aphtha in the erosive fold (arrows ⇒). (b) The Bauhin valve was edematous (arrows →)

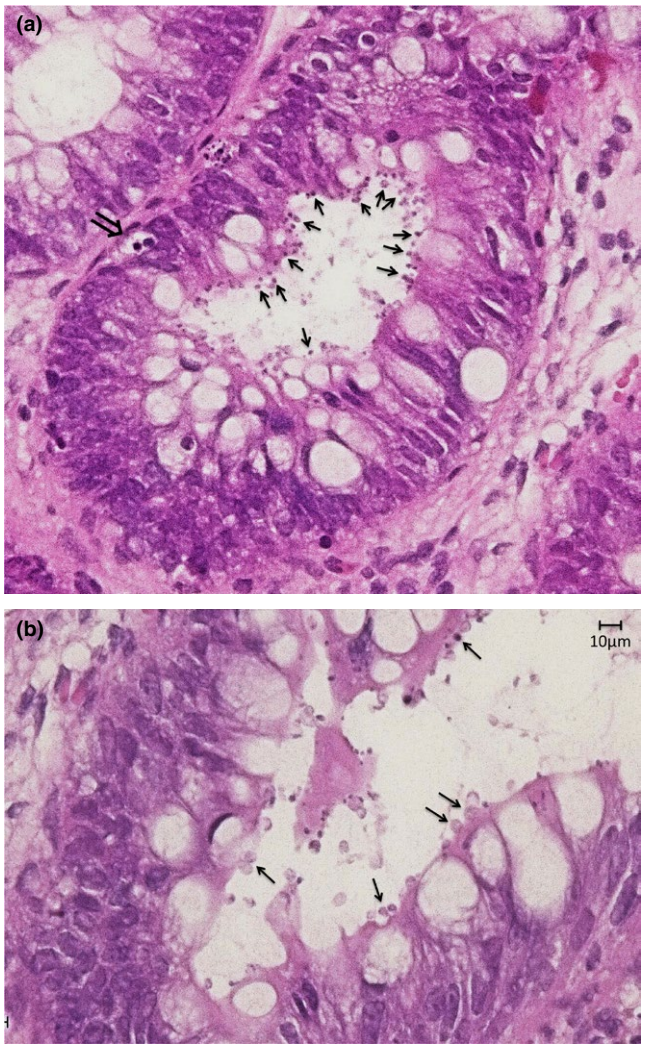

FIGURE 2 (a, b) Histopathology of the colon biopsy. A colonoscopy was performed on day 82. Biopsy samples were obtained from the edematous lesions in the Bauhin valve as shown in Figure 1b. Hematoxylin and eosin staining. Original magnification was 100×. Bar indicates 10 μm. (a) Small spherical parasite forms were distributed along the luminal surface of epithelial cells (arrows →). Apoptotic bodies in the crypt epithelium, which are characteristic of GVHD, were observed (arrow ⇒). (b) The images present different details from the same biopsy. Small spherical particles on the epithelial surface (arrows →)

was observed (Figure 1a and b). Biopsies of the Bauhin valve demonstrated findings consistent with mucosal apoptosis and inflammation as observed in acute GVHD; however, small spherical particles were densely aligned along the luminal surface of the epithelial cells, and *Cryptosporidium* oocysts were suspected (Figure 2a and b). Reevaluation of the biopsies obtained on days 39 and 68 also revealed the presence of the same organism, but not on day 20. The same organism was also noted on the surface of the duodenal epithelial cells. Stool samples were positive for *Cryptosporidium* based on a direct fluorescent-antibody assay. A genotype analysis was performed for the surveillance of infectious disease and confirmed infection with *Cryptosporidium meleagridis*. We finally diagnosed the patient as having cryptosporidiosis.

We initiated anti-parasitic therapy with 500 mg/day oral azithromycin and 1500 mg/day paromomycin and tapered PSL and MMF to restore her immune function. Her symptoms gradually improved 3 months after the initiation of anti-parasitic therapy. We performed a colonoscopy to assess the presence of oocysts and GVHD. The intestinal biopsies demonstrated slight mucosal inflammation without oocysts nor GVHD.

Her lymphocyte counts in complete blood counts decreased because of the chemotherapy and prolonged immunosuppressive therapy. The cluster of differentiation (CD) 4-positive cell counts before and 3 months after HSCT were 50×10^6/L and 9×10^6/L respectively. The CD4-positive cells slightly recovered after the tapering of the immunosuppressive therapy to be 48×10^6/L 7 months after HSCT.

2 | DISCUSSION

Cryptosporidium spp. can contaminate natural water sources and infect epithelial cells in the digestive tract of vertebrates through contaminated food and water. There are over 20 genotypes of *Cryptosporidium* spp., and *Cryptosporidium hominis* and *Cryptosporidium parvum* represent the most common species that infect humans. *Cryptosporidium meleagridis* typically infects birds but occasionally infects immunocompromised hosts.

Although *Cryptosporidium* infection causes self-limited diarrhea in immunocompetent hosts and is prevalent in developing countries, it causes life-threatening diarrhea in immunocompromised hosts.[1-7] There are a few reports of mass infection of *Cryptosporidium* in Japan, but cryptosporidiosis in allo-HSCT has not been reported in Japan, based on a literature search. A few disseminated cryptosporidiosis cases have been reported in hospitalized post allo-HSCT patients during treatment of acute GVHD, similar to our patient.[8-10] In these cases, *Cryptosporidium* was suggested to infect patients latently before hospitalization and disseminate systemically after extensive immunosuppressive therapy. The prevalence of cryptosporidiosis after allo-HSCT has been prospectively studied in a single center in France.[11] In this study, investigators identified *Cryptosporidium parvum* in 5 of the 52 patients who presented with diarrhea at a median of 503 days (range 20-790) after allo-HSCT. The patients without cryptosporidiosis exhibited significantly higher CD4-positive cell counts compared with those with cryptosporidiosis (median 496×10^6/L, range: 40-3400×10^6/L and median 60×10^6/L, range: 0-234×10^6/L respectively). This report suggests that cryptosporidiosis is not an extremely rare comorbidity in allo-HSCT, even in developed countries.

As we experienced with our patient, cryptosporidiosis after HSCT is occasionally difficult to diagnose at an early time point and may be overlooked because of overlapping symptoms and its similarity to acute gut GVHD with respect to clinical and endoscopic manifestations.[9,10] Although the intestinal biopsies suggested acute GVHD, the detection of oocysts residing on the intestinal mucosa led to a final diagnosis of cryptosporidiosis. Although cryptosporidiosis has not been regarded as a common cause of diarrhea after allo-HSCT in Japan, it should be considered as a comorbidity after allo-HSCT in patients on immunosuppressants with severe intractable diarrhea.

CONFLICT OF INTEREST

All authors declare no conflict of interest.

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