Digestive Cryptosporidiosis in an Allogeneic Hematopoietic Stem Cell Transplant Recipient: A Case Report

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Abstract

Cryptosporidium has emerged as a major cause of diarrheal illness worldwide, especially among young children. Cryptosporidiosis infection is increasingly recognized as a major cause of diarrheal disease worldwide in all age groups. The species most commonly involved in human infections are: Cryptosporidium hominis, which infects humans and cattle, and Cryptosporidium parvum, which infects humans and many animals, such as cattle, although infection with unusual species and genotypes occurs in both immunocompetent and immunocompromised populations. A broad range of subjects can be affected, including immunosuppressed patients and children, especially in developing countries. Sporadic or outbreak cases are also observed in immunocompetent individuals. Symptoms of the disease are diverse: 90% of patients experience diarrhea, which is often associated with other gastrointestinal symptoms such as vomiting, nausea or abdominal pain. Asymptomatic infections are also reported. In immunocompromised individuals, such as patients receiving immunosuppressive drugs and Acquired Immunodeficiency Syndrome (AIDS) patients with low CD4 lymphocyte counts, cryptosporidiosis is often chronic, leading to severe weight loss and cachexia. Cryptosporidium species have been reported to be resistant to a wide range of disinfectants and antiseptics, so timely and accurate diagnosis is of clinical importance, particularly in immunocompromised individuals. Currently, very few drugs are active against Cryptosporidium and none are curative: the only antiparasitic drug proven to be effective in severely immunocompromised patients and children is nitazoxanide and especially a reduction of immunosuppressive therapy.

Keywords: Cryptosporidium; Stem cell transplant recipient

Introduction

Cryptosporidium infection is increasingly recognized as a major cause of diarrheal disease worldwide in all age groups. The species most commonly involved in human infections are: Cryptosporidium hominis, which primarily infects humans, and Cryptosporidium parvum, which infects humans and cattle. Cryptosporidium hominis has been reported to be resistant to a wide range of disinfectants and antiseptics, so timely and accurate diagnosis is of clinical importance, particularly in immunocompromised individuals. Currently, very few drugs are active against Cryptosporidium and none are curative: the only antiparasitic drug proven to be effective in severely immunocompromised patients and children is nitazoxanide, while no drugs have been demonstrated to be effective in severely immunocompromised patients. Protozoal infections are generally rare, but life-threatening diseases have been reported in immunocompromised patients. Graft-Versus-Host-Disease (GVHD) is a dreaded complication in graft recipients and the possible development of GVHD is carefully monitored by physicians. We report a case of post-HSCT Digestive Cryptosporidiosis (DC) with delayed diagnosis probably due to its similarity with the clinical features of acute gastrointestinal GVHD.

Case Presentation

A 66-year-old man, living in a rural area, was admitted to our institution for follow-up of essential thrombocytopenia discovered at the time of myocardial infarction. He was treated with hydroxyurea. Thrombocytopenia had progressed to myelofibrosis and finally acute myeloid leukemia. The patient received an induction course of chemotherapy with 3 days of idarubicin 12 mg/m²/d and seven days of cytarabine 200 mg/m²/d. Unfortunately, chemotherapy was complicated by neutropenic colitis with severe denudation and a perforation requiring colostomy. Hematologic reconstitution was not observed after this treatment and bone marrow biopsy showed a gelatinous marrow without blast cells and persistent severe myelofibrosis. Due to persistence of neutropenia and the patient’s good general condition, the patient was selected for allogeneic Hematopoietic Stem Cell Transplantation (HSCT). One month before the graft, the patient developed a non-febrile but profuse diarrheal episode with nausea that responded favorably after several days of symptomatic treatment. No bacterial pathogens or Clostridium difficile toxin A were detected in the stool sample. Previous diarrheal episodes in the family were reported by the patient, but no stool parasitologic examinations were performed during these episodes. A sequential conditioning regimen was performed, as for refractory acute leukemia, consisting of clofarabine 20 mg/d and cytarabine 1g/m²/d at day-12, -11 and -10, cyclophosphamide 60 mg/kg at day-6, busulfan 3.2 mg/kg/d at day-5 and -4 and thymoglobulin 2.5 mg/kg/d at day-3 and -2. GVHD prophylaxis consisted of Ciclosporin A and mycophenolate mofetil starting from day-1. At day-4, he presented Escherichia coli bacteremia which was treated by piperacillin/tazobactam. At day+2, Enterococcus faecium bacteremia was
digested, requiring the addition of vancomycin. At day +4, the patient again experienced watery diarrhea for which screening for C. difficile toxin A was negative. On day +8, abdominal computed tomography was performed due to suspected colitis and revealed lesions that could be attributed to GVHD. The first signs of recovery aplasia were observed on day ±12, but complete recovery was only achieved on day ±42. Colonoscopy colposcopy performed on day ±14 was not suggestive of acute intestinal GVHD, but histologic examination of biopsies was not consistent with the macroscopic findings, making it difficult to confirm or exclude GVHD. Virologic studies on biopsies were negative, while bacteriologic examinations revealed E. coli and E. faecium that could have been responsible for bacterial colitis. However, no improvement was observed after appropriate antibiotic therapy. The diagnosis of GVHD was therefore adopted and corticosteroid therapy (2 mg/kg/day) was initiated on day ±19. Ciclosporin was stopped at the same time due to impaired renal function. After a brief and slight digestive improvement, diarrhea recurred on day ±24. Colonoscopy with intestinal biopsies for histologic examination was performed on day ±32. The histologic features were consistent with the presence of Cryptosporidium sp on the surface of the colonic epithelium (Figure 1).

![Image](arrows), 200 x magnifications and HES stain.

**Figure 1**: Endoscopic biopsy of colonic epithelium showing cryptosporidial trophozoites attached to the epithelial cell surface (arrows), 200 x magnifications and HES stain.

Parasitologic stool examination using a qualitative immunochromatographic assay (ImmunoCardSTAT! Meridian Bioscience, Inc., USA) and Ziehl-Neelsen acid-fast staining revealed Cryptosporidium copro-antigen and oocysts. Stool parasitologic examination on day ±35 therefore confirmed the histologic findings suggesting digestive cryptosporidiosis. Molecular characterization of Cryptosporidium oocysts using PCR targeting the most polymorphic region of the 18S rRNA gene and DNA sequencing revealed Cryptosporidium hominis. A course of oral nitazoxanide (Alinia®), 500 mg × 2/d for 3 days) was started on day ±42 and repeated 2 weeks later and steroids were concomitantly tapered. The patient was discharged on day ±45 with no real improvement of his digestive disorders. He was readmitted on day ±54 with septic shock due to Escherichia coli, successfully treated with appropriate antibiotics. Clinical and parasitologic improvement of digestive cryptosporidiosis was observed on day ±80, as cryptosporidium oocysts were no longer detected in stools and diarrhea had resolved.

**Discussion**

Cryptosporidium infections obviously do not represent a major public health threat in developed countries, although recurrence of gastrointestinal symptoms due to Cryptosporidium is frequently reported, for example in the Milwaukee outbreak in 1993 [5] and in sporadic cases in Europe. In most sporadic cases, the source of infection is difficult to ascertain as many risk factors are commonly encountered in everyday life. Several factors facilitate transmission of Cryptosporidium and account for the propensity to cause large-scale outbreaks of diarrhea: i) Cryptosporidium can infect many mammalian species. It is frequently identified in farm animals, particularly calves, and in domestic animals; ii) oocysts are very resistant and can conserve their infectivity in moist environments for a long time; iii) Cryptosporidium genus is composed of a large number of species, several of which can infect humans; iv) the infectious dose is very low, and infected individuals excrete large numbers of oocysts, up to 108 in a single day [6]. Cryptosporidiosis particularly affects children under four years of age. A high incidence of the disease in this age group has been reported in Canada [7], the United States [8], New Zealand [9] and Europe, particularly in England, France and Wales [10,11]. This high incidence could be due to the fact that physicians usually pay particular attention to diarrhea in children, thereby increasing the chance of detecting and diagnosing Cryptosporidium. During the 1980s, severe cryptosporidium infection was increasingly identified in patients with AIDS [12]. It is considered to be an opportunistic pathogen in immunocompromised hosts and has also been reported in association with primary immunodeficiencies [13], post-transplant immunosuppression [14], leukemia, and lymphoma [15,16]. The case reported here concerns gastrointestinal disorders in an allogeneic HSCT recipient. As is often the case, in contrast with bacterial and viral agents, parasites are less frequently considered by physicians as a potential cause of diarrhea particularly in immunocompromised patients. No stool sample was therefore sent to the parasitology laboratory for examination, which probably allowed earlier diagnosis. A bacterial cause for this diarrheal episode prior to HSCT. Appropriate antibiotic treatment was initiated after obtaining the results of laboratory investigations. However, the gastrointestinal disorders persisted until and after transplantation, suggesting post-graft-colitis and therefore possible GVHD. However, colonoscopy, histologic examination of intestinal biopsies and the patient’s clinical features did not allow a definite diagnosis of GVHD. This confusion with possible GVHD delayed the diagnosis and management of DC. The diagnosis of DC in HSCT recipients can be difficult due to confusion between digestive GVHD and DC, as DC can mimic chronic intestinal GVHD and the two diseases can coexist. A careful differential diagnosis between these two diseases is essential in these patients to ensure appropriate treatment, as the treatment of DC consists of a reduction of immunosuppressive drugs and specific therapy, whereas acute GVHD requires intensification of immunosuppression. In the present case, the delayed diagnosis of DC was based on histologic examination of colonic biopsies on day ±32. Review of the histology slides obtained on day ±14 by an experienced histologist revealed that parasites were already present. As discussed elsewhere [17], recovery from cryptosporidiosis is mainly due to recovery of the immune system. In our patient, complete clearance of Cryptosporidium was obtained on about day ±116 following a reduction of immunosuppressive therapy, improvement of the WBC count (2000/mm³ including 200/mm³ lymphocytes) and antiparasitic therapy. In transplant recipients on long-term immunosuppressive therapy, it is also essential to identify...
the source of contamination to ensure its eradication. However, an environmental investigation in the patient's home is not always easy to perform. The only relevant information concerning our patient was that he lived in a rural area but with no close contact with domestic animals.

This case highlights the need to consider spore-forming protozoa as potential causes of diarrhea in HSCT recipients. The incidence of parasite-related diarrhea in these patients is probably underestimated due to the fact that, in contrast with bacterial and viral agents, parasites are less frequently considered by physicians as a potential cause of diarrhea. Clinicians should therefore systematically perform screening for spore-forming protozoa in all patients with persistent or acute watery stools. Biopsies performed during gastrointestinal endoscopy should be specifically stained and examined by a pathologist experienced in intestinal parasite infections.

References