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Case Report

Cryptosporidiosis, an Uncommon Complication after Allogeneic Stem-Cell Transplantation

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Keywords
Cryptosporidiosis · Allogeneic stem-cell transplantation · Diffuse large B-cell lymphoma

Abstract
Parasitic infections by Cryptosporidium species are rare but can be life-threatening disease after allogeneic stem-cell transplantation (allo-SCT). Here, we reported a case of cryptosporidiosis occurring after a reduced-intensity conditioning and allo-SCT in a 64-year-old farmer with diffuse large B-cell lymphoma. Around day 70 after allo-SCT, he presented with diarrhea attributed to graft-versus-host disease (GvHD) and was treated with immunosuppressive therapy. Due to the patient's worsening clinical condition, a biopsy review was performed, revealing evidence of cryptosporidiosis. Therefore, immunosuppressive therapy was progressively decreased, and antimicrobial therapy including paromomycin and azithromycin was initiated. Following an increase in diarrhea, a second-line treatment with nitazoxanide was administered, resulting in gradual improvement of symptoms. However, recurrence of cryptosporidiosis occurred despite treatment with paromomycin 6 months after transplant and after an episode of GvHD recurrence and colic cytomegalovirus reactivation. Antiparasitic treatment was stopped and azithromycin and rifaximine were started. Immunosuppressive therapy was also reduced. The good clinical evolution allowed for the cessation of all medications. In conclusion, Cryptosporidium infection can complicate allo-SCT and be mistaken for GvHD at the clinical and histologic levels. Early and accurate diagnosis is all the more important as the therapeutic approach for the two conditions is opposite: reduction versus intensification of immunosuppressive therapy. Nitazoxanide, paromomycin, and azithromycin are the first therapeutic options.

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Introduction

The differential diagnosis of diarrhea after allogeneic stem-cell transplantation (allo-SCT) includes acute graft-versus-host disease (GvHD), infections, chemo- or radiotherapy toxicities, medications, neutropenic enterocolitis, and posttransplantation lymphoproliferative disease. The most common infections are caused by *Clostridium difficile* [1], cytomegalovirus (CMV), rotavirus, adenovirus, and enteric pathogens. Parasitic infections by Cryptosporidium species are rare but can be life-threatening disease in immunocompromised patients [2, 3]. The asymptomatic phase of the cryptosporidiosis makes the diagnosis more difficult after allo-SCT. The histologic diagnosis of gastro-intestinal cryptosporidiosis is challenging because of the presence of apoptotic crypt cells, which are also found in GvHD and CMV infection [4]. Cryptosporidiosis is confirmed by the presence of cryptosporidial organisms in the lumen of the gut. Therefore, Cryptosporidium infections can lead to false-positive diagnosis of GvHD, resulting in incorrect treatment. Intensification of the immunosuppressive therapies is detrimental in cases of cryptosporidiosis. Prompt recognition and appropriate treatment are necessary. Given the rarity of the condition and diagnostic difficulties, it is relevant to report the case of cryptosporidiosis occurring after allo-SCT.

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A 64-year-old farmer had a history of marginal zone lymphoma and had undergone several lines of treatment, including splenectomy, chemotherapy, and autologous SCT, due to multiple recurrences of the disease (shown in Fig. 1). He experienced a fourth relapse, which transformed into diffuse large B-cell lymphoma (DLBCL) non-GC, Ann Arbor stage IV, R-IPI 3/5. A complete metabolic response was achieved with loncastuximab tesirine and ibrutinib as part of a clinical trial. Unfortunately, 7 months after starting this treatment, he had a new relapse of DLBCL but was able to control it with salvage chemotherapy using R-ICE and R-methotrexate. He then underwent an HLA 11/12 unrelated allo-SCT after reduced-intensity conditioning with fludarabine and melphalan. GvHD prophylaxis included thymoglobulin, tacrolimus, and MMF. Around day 70 after the allo-SCT, he presented with diarrhea, and stool analysis for *Clostridium difficile*, enteric pathogens, viruses (adenovirus, rotavirus, norovirus), and parasites were negative. PCR CMV in the blood was also negative. In the hypothesis of GvHD, he was hospitalized for high-dose corticosteroids in association with tacrolimus and topical beclomethasone. As is customary in the context of diarrhea following allo-SCT to exclude GvHD, rectoscopy with colon biopsies confirmed acute GvHD stage 4, grade 4 severity, with no evidence of CMV colitis. Despite 1 week of systemic corticosteroids, the patient's symptoms worsened (abdominal pain and diarrhea increased), and etanercept 25 mg twice a week was started, but without the expected efficacy. Thymoglobulin was administered on day 83 due to the patient's clinical condition worsening, as the CT scan still showed severe colitis, and stool analyses remained negative. Due to the patient's poor clinical evolution, a biopsy review was performed, and evidence of cryptosporidiosis was revealed (shown in Fig. 2).

Therefore, methylprednisolone, topical beclomethasone, etanercept, and thymoglobulin were stopped on day 83, and tacrolimus was continued targeting a lower seric level of 8 µg/L. Paromomycin (500 mg four times daily) and azithromycin (500 mg once daily) were initiated. Nitazoxanide (1,000 mg twice daily) was administered as second-line treatment for 14 days due to worsening diarrhea (shown in Fig. 3). A gradual improvement in symptoms was observed. Methylprednisolone 4 mg was resumed on day 96.

On day 114, colon biopsies were carried out due to recurrent diarrhea and revealed grade 3, stage 2 GvHD colitis but no evidence of cryptosporidiosis. Immunosuppressive treatment

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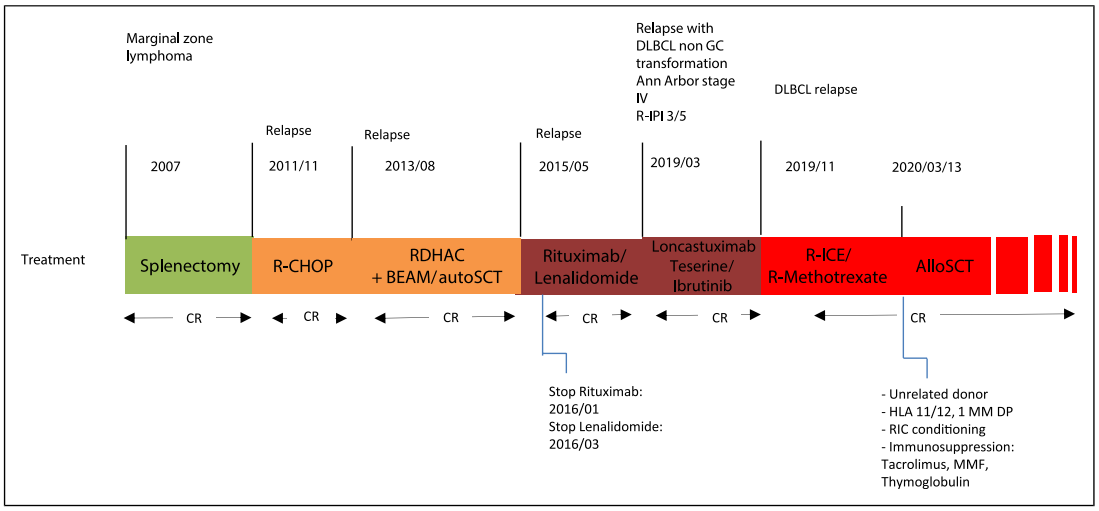

Fig. 1. Evolution of relapses and treatment. CR, complete remission.

was intensified by adding methylprednisolone, topical beclomethasone, and everolimus 0.5 mg twice daily to the existing regimen of tacrolimus and antiparasitic treatment, resulting in clinical improvement and subsequent discharge from the hospital.

On day 148, the patient was readmitted to the hospital due to colonic CMV reactivation. Diagnosis was confirmed through blood CMV PCR and colon biopsies. Ganciclovir was administered, followed by valacyclovir. Paromomycin monotherapy was continued while no modification was made to the immunosuppressive therapy.

At 6 months after the transplant, the patient had a recurrence of cryptosporidiosis, presenting with approximately 8 episodes of diarrhea per day. The diagnosis was confirmed by stool analysis and colon biopsies, and paromomycin was discontinued. Azithromycin (500 mg once daily) and rifaximine (550 mg twice daily) were initiated. Immunosuppressive therapy was further reduced and ultimately stopped.

Currently, the patient is living at home without any disease recurrence, exhibiting normal bowel movements, and having good performance status. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000531571).

Discussion

Parasitic infections caused by Cryptosporidium species are generally self-limited in immunocompetent hosts but can result in life-threatening disease in the case of immunodeficiency [5, 6]. This case demonstrates the diagnosis, treatment, and outcome of cryptosporidiosis after allo-SCT for a relapsed DLBCL. Cryptosporidiosis of the digestive system occurs in patients with profound cellular and humoral immunodeficiency, such as those with AIDS or patient undergoing ATG conditioning regimen for allo-SCT. Infection with Cryptosporidium can account for up to 9.6% of all diarrheal diseases after allo-SCT [3].

In this case, the diagnosis of cryptosporidiosis was complicated by the initial clinical presentation and the histological lesions, which were identical to GvHD. Apoptotic epithelial cells and lamina propria inflammatory infiltrate with polymorphonuclear neutrophils are nonspecific and are seen in both GvHD and cryptosporidiosis [7]. Stool analyses were negative, and no PCR was performed. The systematic use of PCR for screening patients after

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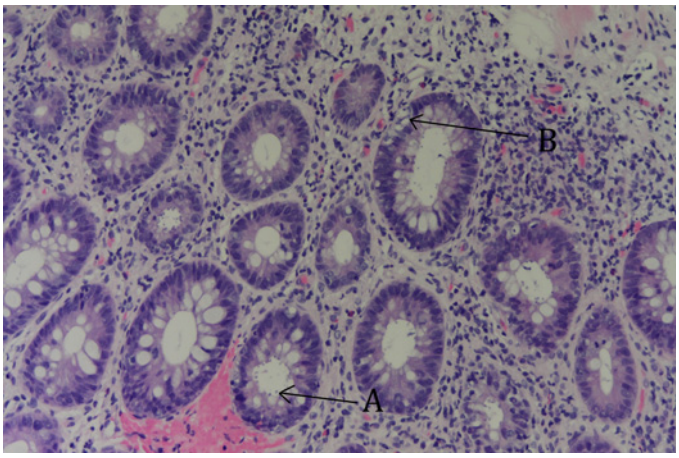

Fig. 2. Colonic biopsy (hematoxylin-eosin). A: Cryptosporidiosis. B: Apoptotic cells.

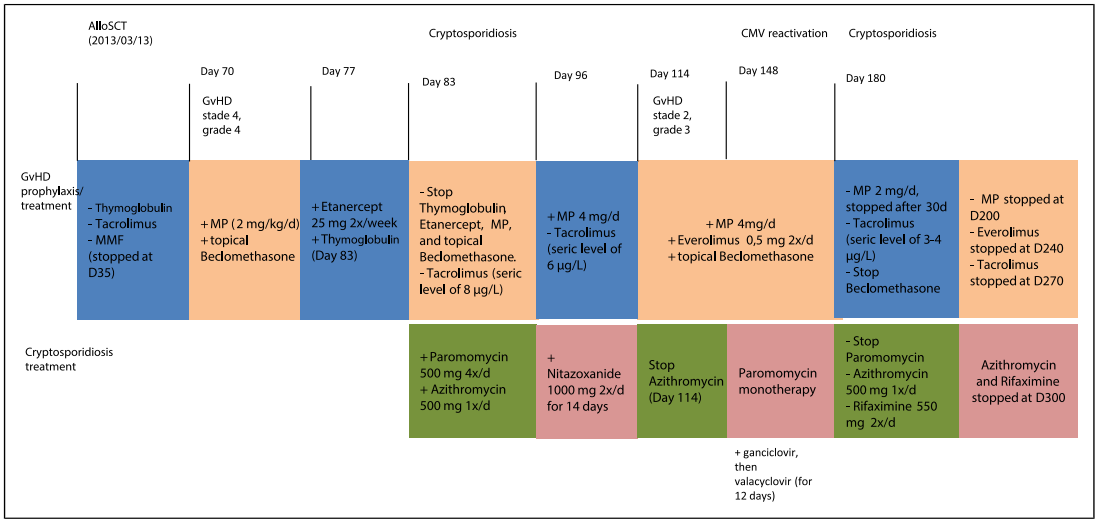

Fig. 3. Cryptosporidiosis evolution. MP, methylprednisolone.

allo-SCT in case of diarrhea, as proposed in immunocompromised children, could help in earlier diagnosis [8]. This specific infection should be investigated in particular population, especially in the context of diarrhea after allo-SCT. In this case, the patient was a farmer from a rural area, and had contracted cryptosporidiosis through his cattle breeding.

In patients undergoing SCT with prolonged lymphocytopenia, cryptosporidiosis is a difficult-to-eliminate disease. There is currently no reliable treatment to eradicate the parasite [9]. Prevention measures should be implemented, including avoiding raw foods and vegetables, drinking boiled or bottled water, and avoiding contact with animal feces. Tapering immunosuppressive therapies is the first-line treatment as antibiotic therapy without restoring immunity is not sufficiently effective for the treatment of cryptosporidiosis [10]. In this case, paromomycin and azithromycin were started as soon as the diagnosis was confirmed, concurrently with reduction of immunosuppressive therapy. Nitazoxanide was introduced as a second-line treatment for 14 days due to an increase in diarrhea, and slowly improved the digestive situation. The patient continued paromomycin after discharge from the hospital.

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A recurrence of digestive cryptosporidiosis occurred 6 months after transplantation, likely due to an increase in immunosuppressive therapy in the context of a relapse of GvHD relapse a few weeks earlier. The recurrence of the disease highlights the difficulty in eradicating cryptopsoridia and emphasizes the need for careful monitoring by physicians.

Conclusion

Infection with Cryptosporidium can be a complication of allo-SCT and can mimic GvHD both clinically and histologically. Prompt and accurate diagnosis is crucial, as the treatment approach for these two conditions is opposite: reducing versus intensifying immunosuppression. Cryptosporidium species have been found to be resistant to many therapeutic agents. Nitazoxanide, paromomycin, and azithromycin are the first therapeutic options.

Statement of Ethics

This case report was conducted in compliance with the ethical principles outlined in the Helsinki Declaration. All authors provided written informed consent to publish this case report. The patient also provided written informed consent to publish the details of his medical history and any accompanying images. Ethical approval was not required for this study in accordance with local or national guidelines.

Conflict of Interest Statement

There is no conflict of interest to disclose.

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Author Contributions

Edwige Boulet and Elodie Collinge drafted the manuscript. Carlos Graux, Anne Sonet, Julien Depaus, Hélène Vellemans, Marc André, and Caroline Fervaille provided critical feedback and revised the manuscript. Carlos Graux, Anne Sonet, Julien Depaus, Hélène Vellemans, and Marc André were involved in the patient's clinical care.

Data Availability Statement

All data generated and analyzed for this case report are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author.

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