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Letters to the Editor

Fecal Microbiota Transplantation as a Salvage Therapy for Concomitant Resistant Digestive Graft Versus Host Disease and Cryptosporidiosis in a Patient Post Hematopoietic Stem Cell Transplant: about a Case

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To the editor.

Chronic myeloid leukemia (CML) is a hematologic malignancy characterized by an uncontrolled proliferation of myeloid cells, particularly neutrophils. It is revealed through the detection of a Philadelphia chromosome (BCR; ABL).

While tyrosine kinase inhibitors have dramatically improved short—and middle-term outcomes, some cases are resistant or relapse.

In these cases, allogeneic hematopoietic stem cell transplantation (HSCT) can be a curative option.

Among the available stem cell sources, umbilical cord blood (UCB) transplantation is a solution for patients lacking donors. However, allogeneic transplants carry a high risk of graft-versus-host disease (GvHD), especially in the gastrointestinal form, which can be life-threatening.

Immunodepressed post-transplant patients, especially those with severe GvHD, are highly susceptible to opportunistic infections such as cryptosporidiosis.[1] Cryptosporidiosis is a parasitic infection of the intestines that leads to enhanced diarrhea, bowel inflammation, and malnutrition. Cryptosporidiosis is a very challenging disease to treat, with standard antiparasitic therapies often proving ineffective or requiring very prolonged courses of treatment.[2]

In this first-ever documented case, we report the successful use of fecal microbiota transplantation (FMT) to treat both corticosteroid-resistant gastrointestinal GvHD and concomitant cryptosporidiosis, leading to significant clinical improvement in a patient post umbilical cord blood HSCT.

Case Presentation. We present the case of a 43-year-old male with a history of CML who underwent umbilical cord blood stem cell transplantation in August 2024 at the University Hospital of Clermont Ferrand.

The patient had a past medical history of CML since November 2022 with NILOTINIB as a first-line treatment. Due to its hematologic toxicity, treatment was interrupted and switched to BOSUTINIB in October 2023.

Again, the tolerance was low with profound cytopenias and the necessity to switch to a third-line treatment with low doses of ASCIMINIB in March 2024.

Finally, as no control of CML could be obtained with TKI, the patient was proposed allograft.

No matched donor was found, and thus, a UCB transplant was performed on June 7th and 10th, 2024, after myeloablative conditioning (THIOTEPA 5mg/kg D-7 and D-6, FLUDARABINE 40mg/m2/j D-5 to D-2, BUSULFAN 130mg/m2 D-5 to D-3 and rabbit anti-thyroglobulin D-3 and D-2).

In post-aplasia recovery, on June 21st, he developed hepatic cholestasis and cytolysis associated with severe diarrhea exceeding 6 liters per day. Corticosteroids (2mg/kg of Methylprednisolone) were started on June 30th, assuming these alterations were due to early GvHD.

On July 17th, a stool examination revealed parasitic infection with cryptosporidiosis, and treatment with Nitazoxanide (1g/12h) was started on the 19th.

As the liver function tests remained altered, we performed a transjugular biopsy on July 30th, which confirmed hepatic GvHD.

Considering the persistence of diarrhea, we performed a rectoscope on August 7th to investigate the possibility of colonic GvHD associated with hepatic GvHD. The biopsy unveiled cryptosporidiosis rectitis, which was associated with some findings suggestive of GvHD (**Figure 1**).

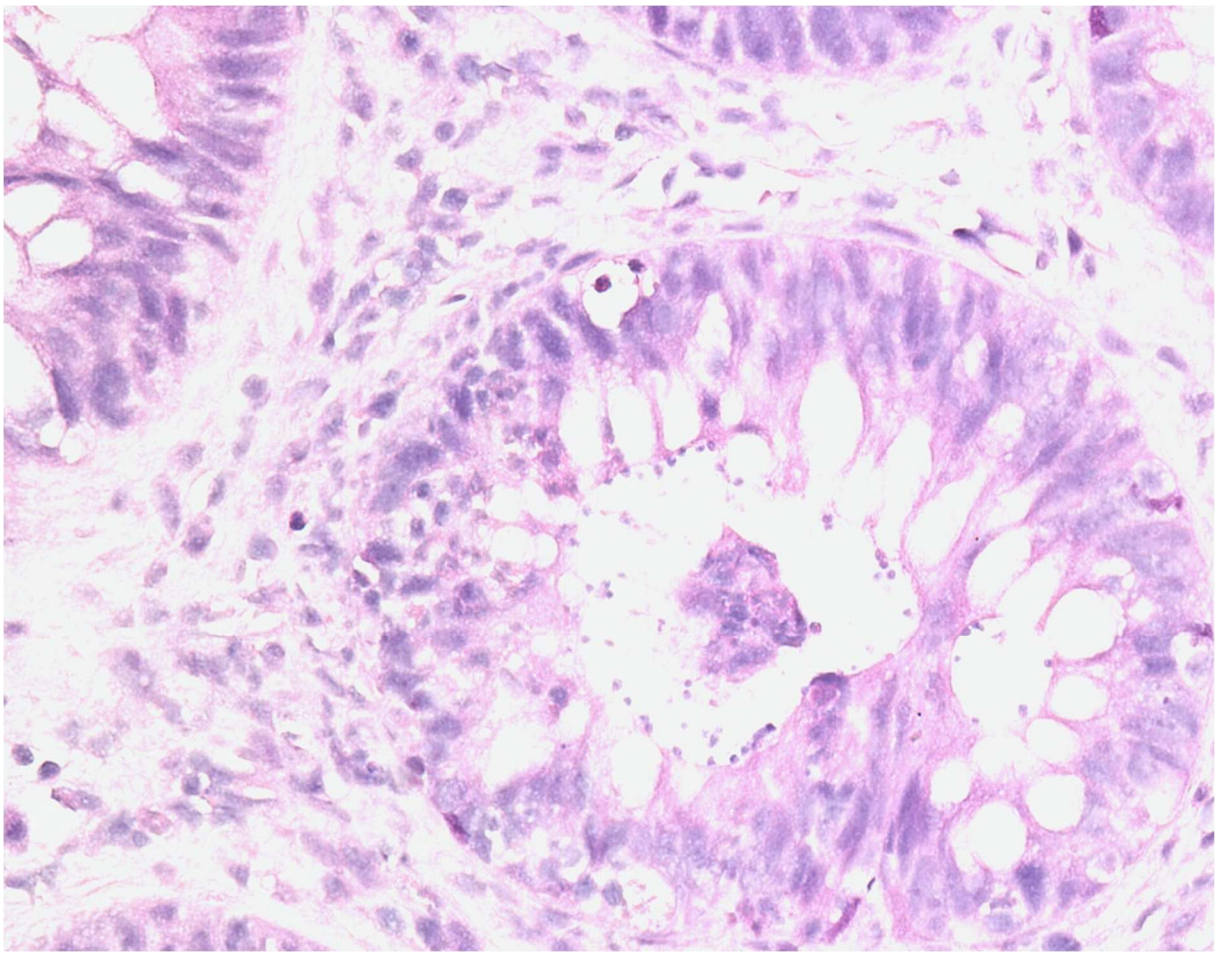

Figure 1. Histological section of a rectal biopsy revealing signs of GvHD (cellular apoptosis) and parasitic infection. Haematoxylin, eosin, and saffron stain, Magnification x400. ⟶ Apoptotic bodies at the periphery of the glands. * Cryptosporidia within the lumina.

Initial management with high-dose corticosteroids proved ineffective, categorizing the GvHD as corticosteroid-resistant. Then, the patient received Ruxolitinib 10mg/12h (08/26) as a second-line therapy, which also failed to reduce the amount of diarrhea but permitted regression of hepatic GvHD.

At the same time, we were unable to improve cryptosporidiosis treatment despite administering Nitazoxanide. Therefore, we discussed the case during a national infectious meeting, which recommended adding Paromomycin (1g/8h) and, afterward, Azithromycin (250mg/12h) as the patient's symptoms persisted.

On the other hand, chimerism at days 30, 45, and 55 was excellent, with 99,5% maintained all along. (BCR;ABL) was not detected anymore

Thus, the allograft proved very effective on the CML.

The clinical situation can be summed up as follows: corticosteroids and Ruxolitinib were ineffective in treating GvHD and, at the same time, favored persistent cryptosporidiosis, which also enhanced chronic diarrhea.

Given the diarrhea's refractoriness to both GvHD therapy and antiparasitic treatment, a multidisciplinary team of hematologists, gastroenterologists, and infectious disease specialists opted for a novel approach: fecal microbiota transplantation (FMT).

The rationale behind this recommendation was the growing evidence supporting the key role of gut microbiota in modulating immune responses and the potential of FMT to restore microbial balance and, therefore, enhance a normal digestive tract's function.[3-6]

After obtaining informed consent, the patient underwent frozen FMT via nasogastric tube (NGT). The donor feces were derived from a healthy screened donor. The transplantation took place twice, on the 18th and on September 20th, 2024 (at 3 months of allograft), and was well tolerated with no adverse effects.

Rapidly after FMT, symptoms improved, with stool volume reduced to less than 1 liter per day and elevation of Cryptosporidium PCR CT (inversely correlated with parasite proliferation).

The patient was discharged from the hospital on October 1st, 2024.

The latest rectoscopy was performed on November 28th and revealed healing of the colic mucosa without any argument for parasitic infection or GvHD.

As the stools' direct examination was negative, we stopped Paromomycin and Azithromycin after November 21st. Nitazoxanide was discontinued after January 30th, 2025, in consideration of a negative cryptosporidiosis PCR and the disappearance of all symptoms.

Finally, the BCR-ABL transcript remained negative at 6 months post graft.

Discussion. This case is particularly significant as it outlines the potential benefits of FMT in addressing both GvHD and concurrent parasitic infections, conditions that are notoriously difficult to treat. Corticosteroid-resistant GvHD is a challenge in HSCT patients, with relentless diarrhea and malabsorption leading to severe denutrition, prolonged in-hospital stay, and thus heightened medical costs. The pathophysiology of gastrointestinal GvHD involves immune-mediated aggression of the gastrointestinal lining, with a sudden influx of inflammatory cells and interleukins resulting in a destruction of the digestive epithelium and, therefore, malabsorption causing diarrhea.

At the same time, these profoundly immunosuppressed patients are at high risk of opportunistic infections such as parasitic infections.

Standard treatments, including increased immunosuppression and antiparasitic drugs, often fail to control symptoms, particularly in cases of cryptosporidiosis, where the parasitic load may persist despite prolonged therapy.

FMT is a novel therapeutic approach. It is traditionally used to treat recurrent Clostridium difficile infections but is increasingly being studied for its role in treating gastrointestinal dysbiosis.

The rationale for FMT in this context lies in its ability to restore microbial diversity and immune homeostasis within the gut. This effect is particularly relevant in GvHD, where the disruption of the gut microbiome exacerbates intestinal inflammation and tissue damage.

Conclusions. The case reported here is groundbreaking as it represents the first documented case of FMT being used to treat both GvHD and cryptosporidiosis simultaneously. The patient's rapid clinical improvement following FMT, with diarrhea volume decreasing from >6 liters/day to less than 1 liter/day within a week, highlights the potential of this therapy to serve as a rescue treatment in similar cases, particularly when traditional therapies fail. This case stands as an example of the potential for microbiome-based therapies in transplant medicine, even if further research is needed to explore the long-term efficacy and safety of FMT in similar settings.

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Competing interests: The authors declare no conflict of Interest.

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