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Eosinophilic Gastroenteritis and Graft-versus-Host Disease Induced by Transmission of Norovirus with Fecal Microbiota Transplant–2

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Abstract

Fecal Microbiota Transplantation (FMT) is one of the emerging strategies against many diseases related directly to the branch of gastroenterology, infectious diseases, hematology or transplantation. Along with mounting new ideas about possible indications for FMT, there are growing challenges as well.

Keywords

Eosinophilic gastroenteritis • Norovirus • Fecal microbiota

About the Study

Fecal Microbiota Transplantation (FMT) is one of the emerging strategies against many diseases related directly to the branch of gastroenterology, infectious diseases, hematology, or transplantation. Along with mounting new ideas about possible indications for FMT, there are growing challenges as well. Our group performed the study concerning the use of FMT as a decolonizing agent in patients colonized with Antibiotic-Resistant Bacteria (ARB) and reported high efficacy (60%-100% decolonization rate after one month) which was also confirmed by other authors [1,2].

Graft-Versus-Host Disease (GvHD) collectively with infections constitutes two main complications after the procedure of Allogeneic Hematopoietic Cell Transplantation (alloHCT) and can occur in 40%-60% of all patients undergoing the procedure [3]. First-line treatment in clinically relevant acute GvHD (aGvHD) includes high-dose steroids, but the main drawback of such therapy is refractoriness or dependency from steroids that is presented by (depending on the severity of the disease or localization) approximately 50% [4]. FMT is one of the second-line options and was documented as an efficient way to reach remission in patients with steroid-refractory GvHD [5].

In this commentary, we describe the main points from the work [1], concerning the case report of eosinophilic gastroenteritis and graft-versus-host disease which was possibly induced by norovirus and *Blastocystis* that were present in the FMT product and patient's gut respectively [6].

The case reports a 36-year-old man with acute myelogenous leukemia, who was admitted to the clinic for qualification to alloHCT, obtained from a matched related donor. The rectal swab for ARB, which is a routine procedure demonstrated gastrointestinal colonization with K. pneumoniae New Delhi metallo-beta-lactamase 1 (NDM-1). As a part of the medical experiment, the patient was offered FMT to help the gut decolonization from ARB. After bowel cleansing using macrogols, the infusion of 100 g/200 ml of fresh feces solution by nasoduodenal tube was carried out on two following days. As the patient did not suffer from gastrointestinal complications and within the next two weeks, three consecutive rectal swabs were proven negative, decolonization was considered. Twenty-three days after FMT the patients started his myeloablative conditioning before alloHCT and underwent transplantation of a peripheral blood stem cell product comprising 5.6 × 106 CD34+cells/kg of body weight. Ten days after alloHCT he developed severe grade III diarrhea. He was diagnosed with norovirus gastroenteritis due to norovirus antigens identified in stool specimens. Because of persisting diarrhea, grade III nausea, weight loss, and rising blood eosinophilia accompanied by skin rush acute Graft-Versus-Host Disease was suspected. The gastro and colonoscopy reviled gastroenteritis and pancolitis and histopathology confirmed features of acute GvHD in the upper and lower gastrointestinal tract. Besides, *Blastocystis* spp. antigen was confirmed in the patient's stool. Acute GvHD grade III was identified according to MAGIC consortium guidelines [7]. After treatment with metronidazole (for *Blastocystis*), intravenous human immunoglobulin infusions (empirically for noroviral infection) and methylprednisolone (for aGvHD) diarrhea ameliorated. We retrospectively tested the FMT material given to patient and found the same geno-group of norovirus as identified in patient's stool. Subsequently, the patient was given a second FMT from another donor (tested negative for norovirus) due to the recurrence of the K. pneumoniae NDM1 colonization and to consolidate the GvHD remission. One day after FMT (9 days after initiation of steroids) the normalization of blood eosinophils count was achieved. K. pneumoniae NDM1 remained decolonized until the last follow-up (6 months).

The total duration of norovirus-induced diarrhea with intestinal aGvHD was 25 days. This case report highlights the microbiota involvement in the aGvHD propagation. Also, indicates the need for more extensive testing of FMT donors, because immunocompromised patients could receive their FMT. Establishing the pathophysiology of norovirus infection is particularly important in the context of immunocompromised patients, as seen in our case the donor was an asymptomatic carrier of norovirus. Normally, gastroenteritis develops after 12 to 48 hours after being exposed to norovirus, but here in the immunocompromised state it started far further. Infection is characterized by an acute inflammatory process involving T cells activation, which leads to the apoptosis of enterocytes in severe cases. Although the intestine is the most frequently occupied location, the contagion of the dendritic cells by norovirus particles gives the ability to spread to mesenteric lymph nodes and peripheral tissues, e.g. the spleen [8]. Graft-versus-host disease after alloHCT is caused by an allogeneic reaction of donor T cells against recipient target tissues. Additional stimulation of T cells by the Norovirus may be a factor enhancing the response of these cells in the aGvHD process. The systemic reaction manifesting as skin rash can potentially be triggered by norovirus particles distributed in the body along with cells of the immune system. The intestinal microbiota and gut dysbiosis is also considered in the context of activation of T cells causing

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acute and chronic GvHD [9].

Conclusion

The aGvHD presentation as eosinophilic enteritis may have been stimulated and exacerbated by the presence of the *Blastocystis* spp. (commonly colonizing human intestines). Inflammatory milieu and increased gut permeability to compounds of dysbiotic intestinal flora might result in sensitization of alloreactive lymphocytes to host antigens triggering acute GvHD with gut and skin predominance. Despite many uncertainties, the presented case indicates a clear relationship between the intestinal microbiota and the occurrence of GvHD.

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