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Fecal microbiota transplantation for the treatment of chronic graft-versus-host disease

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Moderate-to-severe acute graft-versus-host disease (aGvHD) occurs in c.40% of allogeneic hematopoietic stem cell transplantation (allo-HCT) recipients, although the precise incidence varies considerably depending predominantly on the nature of the donor and the method of graft-versus-host disease (GvHD) prophylaxis [1]. Chronic GvHD (cGvHD) is the most relevant cause of late non-relapse morbidity and subsequent mortality (c.25%) following allo-HCT [2]. The incidence of cGvHD is c.50% among all patients following allo-HCT [2]. The first-line treatment of aGvHD consists of steroids, while in the case of cGVHD it consists of steroids given alone or in combination with calcineurin inhibitors (CNI) [1, 2]. While first-line therapy is based on randomized trials, second-line therapy is mostly based on phase II trials and retrospective analyses [2]. The positive news is that new drugs for the prevention and treatment of GvHD have been introduced in recent years [3, 4].

Fecal microbiota transplantation (FMT) has become a standard treatment for relapsing *Clostridioles difficile* infection, and is associated with a cure rate of >90% [5]. It has also been shown that FMT is safe and promotes eradication of antibiotic-resistant bacteria from the gastrointestinal tract in patients with blood disorders [5]. FMT has shown encouraging preliminary and initial clinically relevant results in recent years, and seems to offer hope for patients with GvHD [6, 7].

We present the case of a 16-year-old boy originally diagnosed with pre-B common (+) acute lymphoblastic leukemia, treated according to the ALL-IC-BFM-2009 protocol for an intermediate risk group. At age 18, he was diagnosed with early isolated (marrow) relapse of acute lymphoblastic leukemia (ALL). The patient was treated according to the IntReALL-2010 protocol for a high risk group. The chemotherapy was complicated by profound myelosuppression, severe gastrointestinal mucositis, gastrointestinal obstruction, septic shock, pneumonia, and esophageal ulceration with gastrointestinal bleeding. He was qualified to an HCT procedure, but due to the lack of either a matched or a mismatched unrelated donor, haploidentical peripheral blood stem cell transplantation (haplo-PBSCT) from his mother was performed. Busulfan (3.2 mg/kg/day, days –7 to –4), fludarabine (30 mg/m^2/day, days –7 to –3), and thiotepa (10 mg/kg/day, day –2) were used as a conditioning regimen, while mycophenolate mophetil (MMF, since day +1), post-transplant cyclophosphamide (50 mg/kg/day, days +3, +5) and cyclosporine (since day +5) were used for GvHD prophylaxis. On day +5, the patient received a single dose of rituximab as prophylaxis for Epstein-Bárr virus (EBV) reactivation and post-transplant lymphoproliferative disease. In the early post-transplant period, severe gastrointestinal mucositis and fever were observed. Between days +5 to +15 he was stimulated with filgrastim. Neutrophil engraftment was observed on day +15. He was discharged home on day +28. On day +30, MMF was discontinued. On day +32, aGvHD: skin III [skin rash body surface area (BSA) 60%], intestine grade II. Methylprednisolone 2 mg/kg/day was implemented with a good response and cyclosporine was continued. After day +62 in the stool *Klebsiella pneumoniae* extended-spectrum beta-lactamases (ESBL)+ was cultured repeatedly. Immunosuppressive therapy was tapered and discontinued at day +162. At day +182, was readmitted to hospital with nausea, vomiting, diarrhea, oral mucositis (grade II) and skin rash (60% of his body surface area). In endoscopy, a severe mucositis of the esophagus, stomach and small intestine were present while in histopathology GvHD was confirmed. Methylprednisolone 2 mg/kg/day and sirolimus (with level range 4–6 ng/mL) were applied with a good clinical response and steroids were

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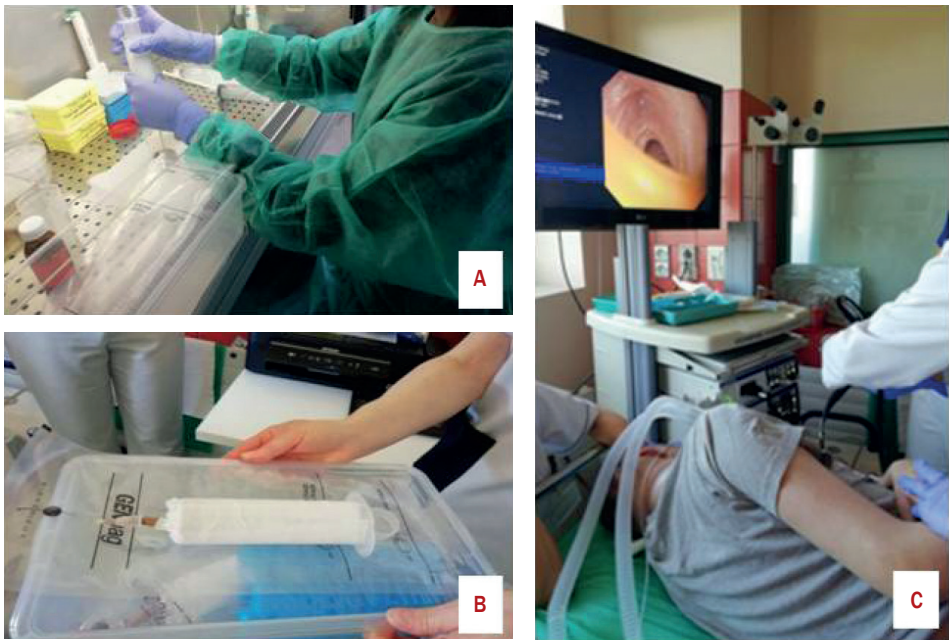

Figure 1. Fecal microbiota transplantation (FMT) procedure: **A, B.** Preparation of FMT donation; **C.** FMT procedure during gastroduodenoscopy under general anesthesia

continuously tapered and stopped (+300). On day +253, sepsis caused by *Klebsiella pneumoniae* ESBL+ with simultaneous urinary tract infection was diagnosed. This infection was successfully treated with meropenem and amikacin. However, on day +262 epididymitis was diagnosed with the need for left orchidectomy with simultaneous creation of a suprapubic cystostomy. In histopathological examination, purulent changes were found in the epididymis and testis with no signs of ALL relapse. After obtaining negative urine cultures and after removal of the cystostomy, two more episodes of urinary tract infection of *Klebsiella pneumoniae* ESBL+ etiology were observed, accompanied by asymptomatic colonization of the gastrointestinal tract with the same pathogen *Klebsiella pneumoniae* ESBL+ and multidrug resistant strain *Enterococcus faecium*. After approval from the Bioethics Committee, FMT procedures via gastroduodenoscopy were performed twice i.e. on days +301 and +303 (Figure 1). No side effect of FMT was observed. Although *Klebsiella pneumoniae* ESBL and multidrug resistant *Enterococcus faecium* were still present in the stool (gastrointestinal tract colonization), we did not observe any other urinary tract infection or sign of GvHD. After day +354, the sirolimus was tapered and discontinued on day +719. The patient remains in a good overall clinical condition with no signs of GvHD.

In conclusion, this case highlights that fecal microbiota transplantation can be a curative option for recurrent GvHD, even though it was ineffective in gastrointestinal tract decolonization from multi-drug resistant bacteria. It is likely that changing the composition of the microbiome not only reduces inflammation in the gut but also induces immunotolerance of recipient cells. It is also possible that it reduces inflammation in the prostate area and prevents further recurrences of urinary tract infection.

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Authors' contributions

KC — sole author.

Conflict of interest

The author declares no conflict of interest.

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform requirements for manuscripts submitted to biomedical journals.

References

1. Holler E, Greinix H, Zeiser R R. Chapter 43. Acute graft-versus-host disease. In: Carreras E, Dufour C, Mohty M, Kröger N. ed. The EBMT handbook: hematopoietic stem cell transplantation and cellular therapies [Internet]. 7th ed. Springer, Cham 2019.
2. Wolff D, Lawitschka A. Chapter 44. Chronic graft-versus-host disease. In: Carreras E, Dufour C, Mohty M, Kröger N. ed. The EBMT handbook: hematopoietic stem cell transplantation and cellular therapies [Internet]. 7th ed. Springer, Cham 2019.
3. Wolff D, Hilgendorf I, Wagner-Drouet E, et al. Changes in immunosuppressive treatment of chronic graft-versus-host disease: comparison of 2 surveys within allogeneic hematopoietic stem cell transplant centers in Germany, Austria, and Switzerland. Biol Blood Marrow Transplant. 2019; 25(7): 1450–1455, doi: 10.1016/j.bbmt.2019.03.003, indexed in Pubmed: 30876928.
4. Styczyński J. Inspiration from Annual Meeting of European Society for Blood and Marrow Transplantation. Acta Haematol Pol. 2023; 54(2): 51–52, doi: 10.5603/ahp.a2023.0021.
5. Bilinski J, Grzesiowski P, Sorensen N, et al. Fecal microbiota transplantation in patients with blood disorders inhibits gut colonization with antibiotic-resistant bacteria: results of a prospective, single-center study. Clin Infect Dis. 2017; 65(3): 364–370, doi: 10.1093/cid/cix252, indexed in Pubmed: 28369341.
6. Biliński J, Jasiński M, Basak GW. The role of fecal microbiota transplantation in the treatment of acute graft-versus-host disease. Biomedicines. 2022; 10(4), doi: 10.3390/biomedicines10040837, indexed in Pubmed: 35453587.
7. Fałkowska A, Jakubas A, Surdacka L, et al. Safe use of fecal microbiota transplant in treatment of graft versus host disease in a 5-year-old child. Acta Haematol Pol. 2023; 54(4): 266–268, doi: 10.5603/ahp.95288.