

Washed microbiota transplantation for the treatment of recurrent fungal infection in a patient with ulcerative colitis

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To the Editor: Long-term use of antifungals can disrupt the balance of fungal community, making the fungal infection treatments more difficult and aggravating colitis in patients. The exploration of fecal microbiota transplantation (FMT) in reducing *Candida* to contain pro-inflammatory immunity induced by gut mycobiota has gained a new appreciation.^[1] The new methodology of FMT was recently coined as washed microbiota transplantation (WMT) based on the automatic purification system and washing process, released by the consensus statement from the Fecal Microbiota-standardization Study Group in 2019.^[2,3] Here, we report a male patient with recurrent fungal infection who was successfully cured by serial WMTs.

A 31-year-old male suffered from recurrent diarrhea for 20 years. He was diagnosed with ulcerative colitis (UC) and psoriasis in 2007. He had the medication history of continuous 5-aminosalicylic acid, a large dose of corticosteroid and anti-tumor necrosis factor (TNF) antibody, but showed no sustained benefits. He finally developed corticosteroid-dependence and secondary loss of response to anti-TNF therapy. He had been using cyclosporine since March 2018 to treat the aggravation of pustular psoriasis and UC, which momentarily improved the skin lesions and diarrhea. Unfortunately, he then suffered diarrhea 10 to 15 times per day since July 2018. The stool was tested positive for Glucan and Galactomannan tests; thus, oral itraconazole was prescribed. However, his intricate fungal infection repeatedly recurred because of his immunocompromised status. He even developed septic shock, with the detection of *Candida glabrata* infection in blood and fecal fungal culture. He gradually lost response to the antifungal treatments and had severe drug-induced liver injury after the usage of 5-month itraconazole (intravenously, and then orally), 6-month fluconazole, and 1-month voriconazole. He was transferred from the previous hospital to our hospital because of the maintained invasive fungal infection and refractory UC.

After admission, the laboratory results showed: elevated white blood cell count, $16.5 \times 10^9/L$; the percent of neutrophilic granulocyte, 89.5%; C-reactive protein (CRP), 20.7 mg/L; and erythrocyte sedimentation rate (ESR), 22 mm/h; significantly reduced plasma cortisol ($<3 \mu\text{g/mL}$) at different points in time; *Clostridium difficile* test (-); hypothyroidism; anti-thyroid antibody (+); stool bacteria culture (-); and stool fungus culture of *C. glabrata* (+). Colonoscopy indicated marked erythema, friability, spontaneous bleeding, and extensive ulcers of the whole colon. Plain computed tomography scan confirmed bilateral femoral head necrosis. The patient was diagnosed as UC (E3, severe activity, Mayo score = 11), *C. glabrata* infection, adrenocortical insufficiency, osteoporosis, femoral head necrosis, psoriasis, Hashimoto thyroiditis, and moderate malnutrition. The ethics of WMT for refractory UC was approved by the Institutional Review Board ([2012] KY No. 015). The patient signed the informed consent of WMT. The five-unit dose of washing microbiota suspension according to WMT protocol was delivered via nasojejunal tube,^[2] which was also used as the enteral nutrition way for him. The donor from Chinese fntBank was screened strictly according to previously reported criteria.^[4] The levels of inflammatory markers rapidly decreased within one week and repeated fecal fungal culture results were negative. However, five times of WMTs did not significantly reduce the stool frequency. Cyclosporine was then reintroduced again as the step-up FMT strategy, which refers to the combination of FMTs followed by immunosuppressants.^[5] The stool frequency decreased to twice per day 2 weeks later. Biochemical examination, blood routine examination, CRP, and ESR monitoring maintained normal. He insisted on entire enteral nutrition, oral cyclosporine, and thalidomide after discharged. The fecal fungus culture remained negative 3 and 6 months after the first WMT. The life quality of this patient showed significant improvement during the 6-month follow-up.

Access this article online

Quick Response Code:



Website:
www.cmj.org

DOI:
10.1097/CM9.0000000000001212

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Chinese Medical Journal 2021;134(6)

Received: 17-06-2020 Edited by: Qiang Shi and Yan-Jie Yin

The comprehensive conditions of this case indicated the necessity of individualized treatments for the patient. Corticosteroid is no longer suitable for him because of the limited efficacy and severe complications. The fast-acting cyclosporine can be used as the switch treatments for patients with severe refractory UC, which was discontinued due to uncontrolled fungal infection for this patient. Multiple WMTs eliminated the contradiction between recurrent fungal infection and immunosuppressive agent usage. Therefore, we reintroduced cyclosporine, for the consideration of this medication alleviated his diarrhea previously. Most of the clinical remission of inflammatory bowel disease (IBD) after FMT has been achieved in combination with immunosuppressive agents, defined as step-up FMT strategy.^[5] This step-up FMT strategy for treating refractory IBD has gained increasing cognition.^[6] Meanwhile, thalidomide can be employed as a treatment option in severe IBD cases by inducing mucosal and histological healing, even in patients with resistance or intolerance to steroids or other anti-TNF agents.^[7] Thalidomide has additional effects, including improving nutritional status, decreasing stool frequency, and maintaining clinical remission in IBD patients,^[7] which need 8 to 12 weeks to take effect. It is necessary to take oral cyclosporine until thalidomide takes effect. The follow-up confirmed that individualized treatment is effective in improving his symptoms and quality of life.

The exploration of gut mycobiota and its correlation with FMT is still in its early stage. The current findings indicated that the inflammatory markers of the patients rapidly decreased after WMT within one week and the repeated fecal fungal cultures were negative during hospitalization and follow-up. This is consistent with the research by Leonardi *et al*^[1], showing a positive outcome of FMT on intestinal inflammation after the reduction of intestinal *Candida* colonization. Several studies supported the effectiveness of FMT plus traditional treatments in inducing clinical improvement or remission for refractory UC when the sole FMT could not rescue the disease.^[4,8] Therefore, step-up FMT strategy might successfully contribute to achieving and maintaining clinical remission in this case.

In conclusion, the multiple WMTs plus cyclosporine might induce clinical improvement in the refractory UC. More attention should be paid to gut mycobiota and the potential role of FMT in recurrent fungal infection treatment in clinical practice.

Declaration of patient consent

The authors certify that they have obtained the patient consent form. In the consent form, the patient has given his consent for his clinical information to be reported in the

journal. The patient understands that his name and initial will not be published and due efforts will be made to conceal his identity, but anonymity cannot be guaranteed.

Acknowledgements

The authors thank China Microbiota Transplantation System for the data about the WMT delivering and evaluation on efficacy and safety. The authors appreciate the kindly help from Cicilia Marcella for professionally English editing.

Funding

This work was supported by a grant from the National Natural Science Foundation of China (No. 81873548).

Conflicts of interest

Fa-Ming Zhang conceived the concept of GenFMTer, transendoscopic enteral tubing, and related devices. Other authors declare that they have no competing interests.

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How to cite this article: Wu X, Cui BT, Zhang FM. Washed microbiota transplantation for the treatment of recurrent fungal infection in a patient with ulcerative colitis. *Chin Med J* 2021;134:741–742. doi: 10.1097/CM9.0000000000001212