Aplastic Anemia in a Patient with Clostridioides Difficile Infection: Successful Treatment with FMT

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Abstract

Aplastic anemia (AA) is thought to be caused by immune-mediated hematopoietic suppression. Its relationship with enteritis has been spotted in several case series including Celiac disease, Crohn’s Disease, and Cronkhite-Canada Syndrome [1-3]. We herein report a case of aplastic anemia with Clostridioides difficile infection (CDI) that was successfully treated with two rounds of fecal microbiota transplant (FMT). After FMT, CDI associated gut microbial pattern shifted towards the donor. Beneficial bacteria gradually took domination, such as Bacteroides and Parabacteroides. Compared with baseline, this patient had lower amount of zonulin released into circulation as well as abated circulative inflammatory mediators after FMT. Eleven months after FMT repeat bone marrow smear returned normal and she was free from immunomodulators. In this study we highlight the role that dysbiosis play in hematopoietic disease. Further evaluation is required in microbiota manipulation’s potential as emerging strategies for hematologic malignancies.

Keywords: Aplastic Anemia; Fecal microbiota transplant; Clostridioides difficile infection

Introduction

Aplastic anemia (AA) is thought to be caused by immune-mediated hematopoietic suppression. Its relationship with enteritis has been spotted in several case series including Celiac disease, Crohn’s Disease, and Cronkhite-Canada Syndrome [1-3]. We herein report a case of aplastic anemia with Clostridioides difficile infection (CDI) that was successfully treated with two rounds of FMT, which might provide new insight into treating this immune-mediated hematopoietic condition.

Case reports

A 20-year-old woman with complaint of chronic non-febrile diarrhea was admitted to a local hospital in 2016. Her endoscopy then revealed mild left-side colitis with biopsy showing infiltration of edematous mucosa by various inflammatory cells. The diagnosis of non-specific colitis was made and she received treatment of mesalamine at 1000mg/day for a month. Her symptoms persisted and she stopped the medication. One year after onset of diarrhea, routine visit revealed progressive normocytic anemia despite a stable nutrition status. Her repeated fecal occult blood ruled out gastrointestinal bleeding. Hemoglobin (Hb) fluctuated between 8.6 to 10.2 g/dL. White blood cell (WBC) count and platelet count were all within normal range. There were no abnormal cells on the peripheral smear analysis. Workup for hemolysis, ferritinemia, plasma vitamins B9 and B12, liver, thyroid function, and renal tests were normal. Plasma adenosine deaminase and plasma proteins electrophoresis were unremarkable. Hemoglobin electrophoresis was also normal. Epstein - Barr virus, cytomegalovirus, and parvovirus B19 serologies were all negative. Bone marrow aspirate and biopsy revealed hypoplastic marrow with no signs of hematological malignancy, such as leukemia or myelodysplastic syndrome. Taken together, these findings led to a diagnosis of
moderate AA that did not require transfusions or substantially increased the risk for serious infections or bleeding. A standard dose of cyclosporine (CsA), with the trough concentration adjusted to achieve a target range of 150-250 ng/mL was given together with anabolic danazol. Her blood count remained stable without the usage of granulocyte colony stimulating factor (G-CSF). For the following 4 years, her diarrhea persisted yet Hb stayed above 10 g/dL. Reticulocyte count, white blood cell (WBC) count and a platelet count were all within normal range. One month before admitted to our department, her diarrhea aggravated to 5-10 times/day with visible mucus and pus. She also presented with elevated white blood cell count of 10.1*10^9/L and an unprecedented dropping of platelets to 56*10^9/L. Our colonoscopy demonstrated patchy, mild erythema and friability of the transverse to sigmoid colon. Using CT-enterography, moderate circumferential thickening and concentric sign was found affecting the descending and sigmoid colon. A positive nucleic acid amplification test (NAAT) for Clostridioides difficile toxin A and B confirm the diagnosis of CDI.

Results and discussion

Two rounds of fecal microbiota transplant (FMT) were then given to this patient in August and September 2020 as described in our similar studies before [4]. A total of 200 g of feces from standard donor were given to the patient via nasal-jejunal tube in 6 consecutive days. Before the first round of transplant, pretreatment with vancomycin (500mg po bid) and Metronidazole (500mg po bid) were advised for 6 days. Bowel cleanse with polyethylene glycol at the end of day 6. The patient’s diarrhea ceased immediately after the first round. Repetitive NAAT one week, one month and three months for Clostridioides difficile after FMT all returned negative. At 3 months after FMT, she was cleared of diarrhea or any other clinical symptoms of CDI. Her blood tests showed anemia resolution and was advised weaned from CsA and danazol. Eleven months after FMT repeat bone marrow spear returned normal and she was free from immunomodulators (Figure 1a and 1b).

Figure 1: Clinical course. (A) The time-line scale from the beginning of disease onset. (B) Key clinical presentations of the patient. (C) Dynamics of circulatory inflammatory mediators Hb, hemoglobin; IL, interleukin; IFN, interferon; TNF, tumor necrosis factors.
AA is reported in several cases of chronic inflammatory enteritis and colitis including Celiac Disease, Crohn’s Disease Ulcerative Colitis, and gastrointestinal polyposis syndrome [1-3,5]. How enteritis and colitis induce AA remains unclear and hypothetical. AA can be a side effect of mesalazine which is a common medication in treating enteritis and colitis [6]. However, this patient only took mesalazine at low dose (1000 mg/d) for one month, thus her anemia can hardly attribute to this medication. An intact, functional intestinal mucosal barrier should prevent the passage of large microbial antigens from the gut lumen into the bloodstream. Zonulin belongs to a family of structurally and functionally related proteins that irreversibly regulate intestinal permeability by modulating intercellular tight junctions. Releasing of zonulin into the circulation can result in permissibility of paracellular trafficking of large inflammatory antigens from the gut lumen into the bloodstream. Increased circulating zonulin level was linked with higher inflammatory mediator level and reported in several auto-immune and hyper-inflammatory diseases such as celiac disease, inflammatory bowel disease and CDI [7]. Compared with baseline, this patient has lower release of zonulin into the circulation (96.42 ng/ml vs 31.5 ng/ml). Correspondingly, she also had decreased LPS-binding protein (LBP) levels after FMT (19.0 μg/ml vs 17.3 μg/ml). Though no compelling causal-effect relationship can be established between zonulin-dependent loss of GI tight junction and onset of AA, reverse of dysbiosis and remedy of tight junction led to the resolution of her hematologic condition. Her circulating inflammatory mediator along the disease course was followed and presented in fig 1c.

AA is a rare hematologic condition characterized by an autoimmune attack against bone marrow precursors mainly caused by self-reactive T-cells, which induces apoptosis of marrow stem cells through direct attack (FAS/FASL) and soluble mediators (IFN-γ and TNF-α) [8]. In a proportion of cases, AA may be secondary to infections such as Parvovirus B19 or hepatitis viruses, possibly due to molecular mimicry, antigen dissequstration, or chronic immune system stimulation as evidenced by high similarity between T-cells receptor variable regions and the molecular structure of CMV, EBV and Influenza A virus [9]. Similarly, in the setting of autoimmune thrombocytopenia, some bacterial infection or colonization had been associated with disease development. Eradication of helicobacter pylori infection led to complete remission of some cases [10]. In one case of ITP, platelets count was reported to be improved by FMT [11]. To illustrate the intestinal microbial composition, Metagenomic next-generation sequencing was thus performed at baseline, 1 day and 1 week after each FMT. In this patient, marked dysbiosis was noticed and was partially corrected after FMT. Our results showed that the fecal microbiota of this patients had overall higher alpha diversity after FMT according to Shannon index. Marked differences at both the phylum and genus levels were observed 8 days post-FMT. Expansion of Clostridia and reduction of Bacteroidia at phylum level after FMT were noticed. Comparing to the donor, the patient’s domination of Prevotella decreased after the first round of FMT, which was reported to mediate mucosal inflammation and lead to systemic dissemination of inflammatory mediators, then in turn may affect systemic disease outcomes [12]. Members of potential beneficial bacteria Bacteroides and Parabacteroides in expanded after FMT, which were complied with previous FMT studies. Their isolations were proved of anti-inflammatory and epithelium reinforcing effect in both vitro and vivo studies [13]. The dominant microbiota of the donor mainly comprised Klebsiella, Enterobacter and Escherichia which didn’t relegated to the recipient. Disparity existed between the donor and recipient, which complied with past evidence that the effectiveness of engrafting of microbiome in the recipient gut depends both on donor microbial species composition as well as the host environment [14]. The Microbial composition of the patient were stabilized 8 days after the first transplant, as visualized by PcoA diagram. The distance from the donor to the recipient shifted dramatically after the first transplant (Figure 2a-d). Temporal pattern of patient’s microbial composition reached plateau after the first transplant. As suggested in previous reports, diverse and robust intestinal microbiota can prevent invading microbes from colonizing the gastrointestinal tract [15]. Function prediction based on KEGG Orthology showed that gene involved in metabolism (carbohydrate and amino acid metabolism, metabolism of terpenoids and polyketides) and environmental information (membrane transport) were significantly up-regulated After FMT (Figure 3).
Figure 2: Microbiota dynamics and weighted UniFrac distance analysis. (A, B) Intestinal microbiota composition at phylum or genus level of the donor and the patient before and after two FMTs. (C) Distance from the donor fecal microbiota of the first FMT. (D) The fecal microbiota dynamics of the patient and the donor. The fecal sample that was obtained before antibiotics treatment was analyzed as “pre” data. The time points such as “post” indicate periods from the initiation of the first or second cycle of FMT.
Figure 3: Function prediction of the patient pre- and post-FMT treatment compared with donor based on KEGG Orthology.
In conclusion, we have reported AA in a patient with definite diagnosis of CDI that was alleviated by FMT. Her hematopoietic anomaly resolved after CDI eradication. We suggest screening for CDI in diarrhea patients with established risk factors including episodic antibiotic therapy, acid suppression, chemotherapy, and immunomodulation. We highlight the role that abnormal, or dysbiotic microbiota play in disease. Further studies into the treatment efficacy, toxicity and their potential promise as emerging strategies for microbiota manipulation in patients with hematologic malignancies is warranted.

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References


