CASE REPORT



Washed microbiota transplantation stopped recurrent sepsis in a patient with myelofibrosis: a case report

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Abstract

Background Sepsis represents the most prevalent infectious complication and the primary cause of mortality in myeloproliferative neoplasms (MPN). The risk of sepsis and the difficulty of treatment are significantly increased in MPN patients due to the need for immunomodulators and antibiotics.

Case presentation On June 9, 2023, a 69-year-old male was admitted to the hospital. Following a battery of tests, the diagnosis of sepsis due to Escherichia coli was ultimately established. The patient was administered amoxicillin clavulanate potassium intravenously. In light of the patient's recurrent sepsis and the likelihood that the source of infection is the intestinal tract, we advised that the patient undergo washed microbiota transplantation (WMT) via a colonic transendoscopic enteral tube (TET).

Conclusions WMT as the new method of fecal microbiota transplantation (FMT) successfully cured the recurrent sepsis in this case, indicating the novel option for challenging the refractory or serious infections.

Keywords Washed microbiota transplantation, Infection, Sepsis, Myeloproliferative neoplasms

Introduction

Sepsis is an acute systemic infection caused by bacteria entering the bloodstream. It often presents with high fever and chills and can easily lead to multiple organ dysfunction syndrome (MODS) or even death [1]. It is the most common infectious complication and the leading cause of death in MPN [2]. The use of immunomodulators such as ruxolitinib, a Janus kinase (JAK)

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³Department of Gerontology, Sir Run Run Hospital, Nanjing Medical University, Nanjing 211166, China inhibitor, has been associated with a decline in immune function, thereby increasing the risk of sepsis in some MPN patients [2]. Furthermore, in order to prevent potential infections, patients with malignant hematological diseases may defensively use antibiotics, which can lead to dysbiosis of the gut microbiota and impaired intestinal barriers. This increases their susceptibility to bacterial translocation (BT) induced enterogenic sepsis [3], which is prone to recurrence and difficult to cure. At present, the predominant clinical treatment modalities for sepsis continue to prioritize antiviral and antibacterial agents. However, there remains a dearth of efficacious interventions for this form of recurrent sepsis.

It has been demonstrated that FMT can restore gut microbiota homeostasis, reduce inflammatory responses, and regulate systemic immunity, effectively treating sepsis and sepsis-induced MODS [4]. The Nanjing consensus



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on methodology of washed microbiota transplantation, developed by Zhang's team, establishes a standard protocol across five key areas: donor screening, washout preparation protocols, storage and transportation, patient preparation, and choice of grafting route, as well as safety management. This consensus specifically addresses the source of the transplantation product, preparation and pre-medication protocols [5]. As the next generation of FMT, WMT not only offers a refined methodology compared to manual FMT but also provides a safe and convenient delivery route [6]. TET refers to colonic transendoscopic tube-delivered enteral therapy. Colonic TET has been successfully used for frequent colonic administration of drugs or multiple FMTs [7]. Our case can serve as a valuable reference for subsequent treatment of recurrent sepsis and refractory infections.

Case report

On June 9, 2023, a 69-year-old male was admitted to the hospital with a sudden onset of high fever and chills, with no other significant symptoms. The patient had been diagnosed with chronic renal insufficiency in 2004, pure erythrocytic aplastic anemia in 2012, and primary myelofibrosis by bone marrow aspiration in 2021. He had recently been taking rucotinib continuously. Upon admission, the patient's temperature was 38.5 °C, reaching 40 °C that evening. The patient was administered xylazine, celecoxib for cooling. Some of the patient's test indicators are as follows (Table 1): The white blood cell (WBC) count was 19.53×10⁹/L, the C-reactive protein (CRP) level was 69.1 mg/L, the procalcitonin (PCT) level was 1.62 ng/ml, and the interleukin-6 (IL-6) level was 803.1 pg/ml, indicating the presence of anemia and bacterial infection. The anaerobic blood culture results indicated the presence of Escherichia coli, and the results of the antimicrobial susceptibility test (AST) indicate that this patient's E. coli infection was susceptible to normal dosing (S) amoxicillin clavulanate potassium. In light of the aforementioned tests, the diagnosis of sepsis due to Escherichia coli was ultimately established. The patient was administered amoxicillin clavulanate potassium intravenously, in conjunction with blood transfusion therapy. The aforementioned treatment regimen was maintained for a period of two weeks, during which time there was a discernible improvement in the patient's indicators.

 Table 1
 The laboratory findings from the patient's initial admission for sepsis

Indicator name	numerical value	Normal value	
White blood cel (WBC)	19.53×10 ⁹ /L	3.5-9.5×10 ⁹ /L	
C-reactive protein (CRP)	69.1 mg/L	0–10 mg/L	
Procalcitonin (PCT)	1.62ng/ml	<=0.05ng/ml	
Interleukin-6 (IL-6)	803.1pg/ml	<=7.00pg/ml	

However, on August 1, 2023, the patient was readmitted to the hospital with symptoms of hyperthermia and chills, and his temperature reached 39.5 °C. The patient's WBC count was 26.01×10^{9} /L, with a CRP level of 67.1 mg/L, a PCT level of 7.851 ng/mL, and an IL-6 level of 140.34 pg/mL. The bicarbonate ion concentration was 19.9 mmol/L, indicative of metabolic acidosis. The anaerobic blood culture vielded a positive result for Escherichia coli. The results of the drug sensitivity experiment were consistent with those of the previous trial (Table S1). The same treatment strategy was employed as in the initial approach, utilising amoxicillin clavulanate potassium IV in conjunction with blood transfusion, in addition to thymus 5 peptide to enhance immunity. The patients exhibited indications of recuperation following a two-week regimen of continuous treatment.

In order to determine the source of infection of the patient's sepsis, we performed sputum culture, routine urine examination, and chest and abdominal CT scan, which revealed that the patient's sputum culture results were negative, there were no bacteria in the urine, and chest and abdominal CT scans did not reveal any lung infection, biliary tract infection, liver abscess, etc. In addition, the patient had no symptoms of abdominal pain and diarrhea, cough and sputum, and dysuria and dyspareunia. In summary, the possibility that the patient had sepsis of enteric origin is the highest, because E. coli of enteric origin does not necessarily cause intestinal symptoms.

In light of the patient's recurrent sepsis and the likelihood that the source of infection is the intestinal tract, we advised that the patient undergo WMT via a colonic TET [8] once the infection had been effectively controlled. The procedure was conducted in the following manner: The enteroscope was advanced to the ileum and retreated for observation, revealing no abnormalities at the ileocecal valve or the end of the ileum. The TET was placed through the endoscopic biopsy orifice to the transverse colon and re-entered the enteroscope. One titanium clip was used to fix the coil of the first station of the TET tube to the ileocaecum and the mucosal folds of the ascending colon (Fig. 1). The in vitro component was secured in the gluteal region. The wash-treated bacterial fluid was delivered directly to the ileocecal portion of the patient's colon via transendoscopic tube injection. Following the initial WMT, the patient developed a low-grade fever. A second WMT was administered the following day, which resulted in the normalization of her temperature without any adverse effects. The patient was discharged on September 9, 2023. A follow-up examination was conducted in February 2024, at which time the patient's family reported that the patient was in stable health and had not experienced any further febrile symptoms.



Fig. 1 Schematic of WMT via a TET

Discussion

Sepsis is a prevalent clinical emergency. The identification of the source of infection and the implementation of targeted treatment strategies are essential for the effective management of sepsis [9]. However, in some cases, the source of infection is challenging to ascertain, and patients present with comorbidities, which may result in recurrent episodes of sepsis and suboptimal outcomes with antibiotic monotherapy. This report presents the initial case of recurrent sepsis in primary myelofibrosis treated with WMT.

The relationship between MPN and sepsis was further investigated through the use of Mendelian randomization. The exposure was MPN with GWAS dataset "ebi-a-GCST90000032" from the ieu open gwas project (htt ps://gwas.mrcieu.ac.uk/). The outcome was sepsis (crit ical care) with GWAS dataset "ieu-b-4982" from IEU as well. A screening threshold of P < 1e-05 yielded 18 SNP loci that were identified as instrumental variables (IVs) (Table S2). Four methods were employed to analyze the causal effect between exposure and outcome: MR Egger

(P=0.488, OR=1.063, 95% CI=0.898-1.258), IVW (P=0.041, OR=1.070, 95% CI=1.003-1.141), Weighted mode (P=0.090, OR=1.104, 95% CI=0.991-1.229), and Weighted median (P=0.048, OR=1.094, 95% CI=1.001-1.196) (Fig. 2A, B,C). The findings indicate that individuals with MPN are at an elevated risk of developing sepsis. The results of the heterogeneity test indicated the absence of significant heterogeneity among the IVs (P > 0.05) (Table S3). The MR-Egger intercept (Table S4) and MR-PRESSO (Table S5) demonstrated the absence of statistically significant horizontal pleiotropy (P > 0.05). The leave-one-out test demonstrated that no single SNP exerted a significant influence on the MR analysis outcomes, thereby ensuring stability (Fig. 2D). The funnel plot exhibited no evidence of bias, thus confirming the robustness of the results (Fig. 2E).

Gut serves as a reservoir for microbiota within the human body. Escherichia coli represents one of the most prevalent microorganisms within the gut. Its presence does not inherently result in the manifestation of intestinal symptoms. However, in this case, dysbiosis of the gut A



Fig. 2 (A): Visualization of the analytical results of Mendelian analysis by forest plots. (B): The causal effect of exposure on outcome was evaluated for each single-nucleotide polymorphism (SNP) estimate and illustrated in the forest plot. (C): The effects of single nucleotide polymorphisms (SNPs) on the outcome variable are plotted against the effects of the same SNPs on the exposure variable. The slope of the line represents the causal association, which differs according to the method employed. (D): A leave-one-out sensitivity analysis was conducted to ascertain whether a single SNP exerted a disproportionate influence on the observed association. The black dots in the forest plot represent the results of individual Mendelian randomization (MR) analyses, with each dot corresponding to a specific single-nucleotide polymorphism (SNP) that has been excluded from the analysis. Additionally, an overall analysis that includes all SNPs is also presented. (E): Funnel plots were employed to evaluate heterogeneity

microbiota, a fragile intestinal barrier, and low immunity may result in bacterial translocation, allowing E. coli to enter the mesenteric circulation and trigger bacteremia or sepsis [10, 11]. This may be the underlying cause of the recurrent episodes of sepsis observed in this patient. It is important to note that, in the absence of overt intestinal symptoms, enterogenic sepsis caused by Escherichia coli can be challenging to diagnose definitively based on the culture results of normal feces. This can make it difficult to identify the primary site for treatment.

The decision to utilize the same antibiotics for recurrent sepsis was based on three primary considerations: (1) While awaiting the outcome of the AST, the patient was treated with amoxicillin clavulanate potassium, which resulted in a notable reduction in symptoms and a return to normal temperature, suggesting that this antibiotic is efficacious. (2) Based on the reference standard set forth by the Clinical & Laboratory Standards Institute (CLSI), the results demonstrated that the E. coli strain present in the patient's bloodstream exhibited susceptibility to all penicillin-class antibiotics, with the exception of amoxicillin. (3) A full course of antibiotics was administered, and the patient's blood culture results became negative prior to discharge. Additionally, the infection markers had returned to normal values. It was therefore concluded that the two infections were caused by the same pathogen rather than being a relapse due to Escherichia coli resistance.

The efficacy of FMT in the treatment of infectious diseases has been demonstrated, including the successful treatment of sepsis of unknown origin and MODS caused by sepsis [12]. In this case, WMT demonstrated favorable therapeutic outcomes in the treatment of sepsis, with the additional benefit of preventing recurrent episodes. WMT may restore the homeostasis of the gut microbiota, reduce the inflammatory response, and modulate systemic immunity [12, 13]. Nevertheless, further validation of these mechanistic studies is required to enhance our comprehension of the interrelationship between gut microbiota and sepsis and to substantiate the clinical utility of such treatments.

Abbreviations

MPN	Myeloproliferative neoplasms
WMT	Washed microbiota transplantation
FMT	Fecal microbiota transplantation
TET	Transendoscopic enteral tube
MODS	Multiple organ dysfunction syndrome
BT	Bacterial translocation
JAK	Janus kinase
AST	Antimicrobial susceptibility test
WBC	White blood cell
CRP	C-reactive protein
PCT	Procalcitonin
IL-6	Interleukin-6
MR	Mendelian randomization
CLSI	Clinical & Laboratory Standards Institute

Supplementary Information

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Supplementary Material 1	
Supplementary Material 2	
Supplementary Material 3	
Supplementary Material 4	
Supplementary Material 5	

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Author contributions

Acquisition of data (TZ, TX), drafting of the article (YY, LW), critical revision of the article for important intellectual content and final approval of the article (QW and MJ). All authors read and approved the final manuscript.

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Data availability

The datasets analysed during the current study are available in the GWAS repository, https://gwas.mrcieu.ac.uk/datasets/ieu-b-4982/. https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST90000032/.

Declarations

Ethics approval and consent to participate

Our study has passed the ethics approval by Sir Run Run Hospital.

Consent for publication

Written informed consent was obtained from the patient for the publication of his clinical details.

Competing interests

The authors declare no competing interests.

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