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Improvement of Good's syndrome by fecal microbiota transplantation: the first case report

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Abstract

Good's syndrome (GS) is a rare primary immunodeficiency defined as hypogammaglobulinemia associated with the presence of a thymoma. Patients with GS usually have increased susceptibility to a wide range of infections, and clinical treatment is a challenge for physicians. Fecal microbiota transplantation (FMT), which is a safe strategy for reconstruction of the gut microbiota, has a positive influence on the treatment of refractory infections such as those in patients with GS. We herein report a case involving a 73-year-old woman who had been previously diagnosed with a thymoma. After thymectomy, she complained of respiratory and gastrointestinal symptoms. Her laboratory analysis strongly suggested GS. Infusion of immunoglobulin and albumin was the only treatment of choice until FMT was considered as an alternative therapy. The patient's manifestations were subsequently relieved, and several FMTs were required to maintain clinical remission. Management of GS remains quite challenging to physicians because of the intricate organ involvement and limited and costly existing therapies. FMT is usually well tolerated by patients, and its cost-effectiveness and safety profile allow it to be considered as an alternative therapy for GS.

Keywords

Fecal microbiota transplantation, Good's syndrome, gut microbiota, hypogammaglobulinemia, thymoma, refractory infection

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Introduction

Good's syndrome (GS) occurs in the presence of a thymoma and manifests as a wide range of chronic, usually refractory symptoms. The etiology of GS remains unclear, but the intestinal infections associated with GS may be related to immunodeficiency, malnutrition, and intestinal villous atrophy.[1,2] The characteristic triad of symptoms (immunodeficiency, intestinal infections, and malnutrition) often renders GS unable to be successfully managed. The classic treatment strategy involves administration of immunoglobulin, albumin, and nutrition replacement therapy. This strategy works by triggering and boosting the depressed immune system secondary to the thymoma to prevent opportunistic infections. Because of the high medical cost and lack of insurance coverage, most patients cannot afford these therapies. Patients with GS have gut microbiota dysbiosis, but this is not the only cause of the disease. The dysbiosis in GS represents the changing status of the gut microbiota during the disease development. Hence, reconstructing the gut microbiota through fecal microbiota transplantation (FMT) may benefit patients.[3] We herein describe a patient who developed GS after thymectomy for treatment of a thymoma, the impact of FMT on the recurring symptoms, and the cost-effectiveness of the therapy. This specific case is being reported to demonstrate that FMT can be considered an alternative cost-effective measure to manage disease when other treatment modalities fail.

Case report

In March 2014, a 70-year-old Chinese woman developed recurrent watery diarrhea with a frequency of 5 to 10 times a day accompanied by indigestion, malnutrition, respiratory tract infections, and weakness. After hospital admission, physical examination and computed tomography revealed an anterior mediastinum space-occupying mass that was diagnosed as a type B3 thymoma by computed tomography-guided percutaneous puncture biopsy. The patient underwent a thymectomy. Colonoscopy performed at that time revealed no abnormalities. One month after resection of the thymoma, she developed lymphatic tuberculosis, for which an anti-tuberculous regimen (isoniazid, rifampin, pyrazinamide, and ethambutol) was administered for 10 months. Additionally, the involved lymph node was resected. During follow-up, she responded well to the anti-tuberculous drugs. In March 2015, she presented in a severely malnourished condition with a body weight of 40 kg and had severe progressive refractory diarrhea despite treatment with dioctahedral smectite, and trimebutine maleate. She had respiratory infections, for which antibiotics and antiviral agents were administered. An analytical study revealed the following: immunoglobulin (Ig) G serum level, 2.28 g/L (reference range, 7.00–17.00 g/L); IgA serum level, 0.59 g/L (0.70–4.00 g/L); IgM serum level, 0.06 g/L (0.40–2.30 g/L); white blood cell count, 5.68×10^9/L ($3.50–9.50 \times 10^9$/L); CD19+ B lymphocyte count, 9/μL (160–350/μL); CD16+/CD56+ natural killer cell count, 203/μL (155–550/μL); CD4+ T-cell count, 285/μL (550–1200/μL); CD8+ T-cell count, 703/μL (380–790/μL); and CD4+/CD8+ T-cell ratio, 0.41 (0.9–2.0). Bone marrow examination revealed active hyperplasia, a myeloid/erythroid ratio of 5.6:1.0, a neutrophilic promyelocyte concentration of 5.2% (0.2%–2.5%), a neutrophilic myelocyte concentration of 16.0% (2.7%–13.0%), and a proerythroblast cell count of 1.2 (0.0–0.8 cells). Studies of human immunodeficiency virus, cytomegalovirus, Epstein–Barr virus, and hepatitis B and C were negative. Immunofixation electrophoresis (IgA + IgG + IgM) results were all negative.

The patient was administered traditional therapy: immunoglobulin and albumin replacement therapy, parenteral nutrition, and probiotics. A short remission period was observed, but this period was followed by a relapse of symptoms. Hypogammaglobulinemia associated with thymoma is an important landmark for the definitive diagnosis of GS. The average length of stay during this 1-year period (2015–2016) was 18.2 days, and the total expenditure was 205,000 CNY.

In February 2016, capsule endoscopy revealed duodenal inflammation. In September 2016, the patient was dependent on immunoglobulin infusion to maintain clinical remission. In the pursuit of a more cost-effective treatment, she was admitted to our department with an increased frequency of diarrhea of 15 times per day for 2 years accompanied with lower limb edema and a relapsing cough. The patient was underweight. Laboratory examination revealed an IgG level of 2.15 g/L (7.00–17.00 g/L), IgA level of <0.27 g/L (0.70–4.00 g/L), and IgM level of <0.17 g/L (0.40–2.30 g/L). The patient had immunodeficiency, anemia, and electrolyte disturbance, and she subsequently received the traditional treatment regimen. The electrolyte disturbance was corrected, and we held an ethics committee discussion about the use of FMT from the national fecal microbiota bank in China (fmtBank) in this case because of failure of the common traditional treatment strategies. The patient was then advised to receive FMT through a mid-gut tube (FMT Medical, Nanjing, China). FMT resulted in relief of the intestinal and respiratory tract symptoms, and a decreased stool frequency was observed without any FMT-associated discomfort such as nausea and vomiting. Despite the patient's persistent immunodeficiency, FMT did not cause any new infections. FMT was repeated through the nasoduodenal tube 48 hours after the first FMT treatment session, and the patients' laboratory tests were repeated. The IgG level had increased to 7.88 g/L (7.00–17.00 g/L), and the IgA and IgM levels remained basically unchanged at <0.27 g/L (0.70–4.00g/L) and <0.19 g/L (0.40–2.30 g/L), respectively. The procedure was repeated every 3 months; at every hospital admission, FMT was performed one to three times depending on the severity of the symptoms. After FMT, the patient discontinued the antibiotics for the pulmonary infections, and the frequency of immunoglobulin infusion also significantly decreased.

In 2017, 1 year after FMT, the patient was admitted for follow-up FMT because of relapse of symptoms with an increased daily stool frequency and a low IgG level of 4.64 g/L (7.00–17.00 g/L). The patient was found to have the same deficiencies as 1 year previously: anemia and hypogammaglobulinemia with a low albumin level. FMT resulted in relief of symptoms and an increase in the IgG level to 11.10 g/L (7.00–17.00 g/L). The cost was lower at 103,432 CNY with an average length of stay of 9 days during that year (Figure 1). Additionally, the patient had a better appetite during the post-FMT follow-up period.

Follow-up and outcomes

In this case, FMT proved to be a good alternative treatment for a patient with GS and refractory infections. This novel therapy not only decreased the frequency of diarrhea but also the incidence of respiratory tract infections experienced by the patient.

The patient underwent follow-up examinations every 3 months, and FMT was repeated when the symptoms relapsed. The patient tolerated the FMT well and showed no adverse effects.

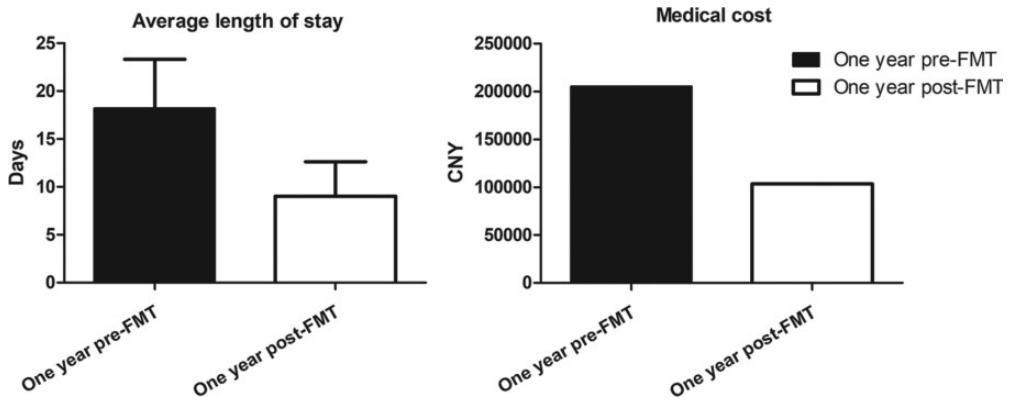

Figure 1. Comparison of average length of stay and medical cost before and after FMT. (a) The average length of stay during the 1-year period after FMT was shorter than that during the 1-year period before FMT, suggesting the efficacy of FMT. (b) The medical cost during the 1-year period after FMT was lower than that during the 1-year period before FMT, indicating the cost-effectiveness of FMT. FMT, fecal microbiota transplantation.

Discussion

Since 1954, GS has been classified as an immune deficiency of adult onset with a CD8:CD4 imbalance, low CD4 count, low to absent B cells, and association with thymoma; however, no diagnostic criteria have been established.[4] The etiology of this immune dysfunction remains elusive. GS can be distinguished from other common immunodeficiencies such as autoimmune enteropathy by the presence of both hypogammaglobulinemia and low B-cell populations. The present report describes an unusual case of GS in which the infectious symptoms and multiple organ involvement persisted after thymoma resection despite adequate traditional therapy.

Diarrhea, which was the main manifestation in our case, is commonly present in 50% of patients with GS.[5] The mechanism by which the hypogammaglobulinemia causes diarrhea in patients with thymoma remains unclear. One hypothesis suggests that it could be due to villous atrophy[6] and that correction of the immune imbalance could benefit patients with GS. Our patient's diarrhea subsided after initiation of intravenous immunoglobulin therapy, indicating that hypogammaglobulinemia was the underlying cause. Furthermore, patients with GS are more susceptible to gastrointestinal infections, but specific pathogens were not reported in most cases,[1] including ours. Other possible etiologic pathogens include *Salmonella* spp., *Giardia lamblia*, and *Cytomegalovirus* spp.[1]

Because of the deficiency of B and T cells, patients with GS are susceptible to a variety of infections including those by *Haemophilus*, *Streptococcus*, *Pseudomonas*, *Klebsiella*, *Bordetella*, *Candida*, *Pneumocystis jirovecii*, and *Giardia*.[1,7,8] In addition to diarrhea, our patient had tuberculosis after the thymoma resection and developed frequent pulmonary infections along with the tuberculosis. Recurrent pulmonary infections are usually caused by bronchiectasis.[9] In this case, the antibiotics used for treatment of the pulmonary infections might have disrupted the gut microbiome, increasing the susceptibility to opportunistic infections.[10]

An alternative treatment strategy is needed for GS. FMT is currently an established treatment modality for recurrent *Clostridium difficile* infection, inflammatory bowel disease, and other complicated diseases.[11–13] We considered this alternative treatment in the present case. After discussion with and approval by the ethics committee of our health care institution, FMT was performed through a nasoduodenal tube to restore the disturbed gut microbiota caused by GS. FMT is used in patients with diseases involving a disturbance in the gut microbiota. The most significant clinical manifestation experienced by our patient was diarrhea. The diarrhea may have been due to an opportunistic bacterial infection (invasion of opportunistic bacteria causes dysfunction of the gut microbiota) secondary to the immunodeficiency or secondary to the increased use of antibiotics, which might have disturbed the normal gut flora and subsequently impaired the mucosal immune response. Importantly, gut dysbiosis is not the only cause of this disease but denotes a change in the status of disease development. This explains why gut microbiota reconstruction can be used to improve the clinical symptoms in patients with GS. FMT curbs the gastrointestinal symptoms by restoring the gut microbiota through different proposed mechanisms, all leading to an increased immune response. Through the gut–lung cross talk, the gut microbiota or its metabolites and components facilitate a greater immune response in both the gut and lung, hence simultaneously relieving inflammatory symptoms in both organs. Moreover, in the present case, we chose a nasoduodenal tube as the delivery route for FMT over other routes because of the patient's poor condition; nasoduodenal tubes are safe because they reduce the risk of aspiration of bacterial fluid, which may exacerbate the patient's pulmonary infections, and are suitable for multiple FMTs because their placement can be maintained for a long period of time.[14,15] After FMT, the patient's intestinal manifestations greatly improved with a decreased frequency of diarrhea per day, and the respiratory manifestations were relieved.

FMT may resolve the gut microbiota dysbiosis and subsequently increase microbiota-derived metabolites such as short-chain fatty acids (SCFAs). SCFAs are a crucial energy source for intestinal epithelial cells and affect the gut morphology and function. They accomplish their role by binding to endogenous receptors such as G protein-coupled receptor (GPR) 41 and GPR43. Previous reports have shown that SCFAs may activate GPR43 or inhibit histone deacetylase to help stimulate regulatory CD4+ T cells, thus protecting against respiratory tract inflammation. Although SCFAs are mainly located in the gut, they can circulate in the bloodstream and influence cells in the surrounding tissues. Trompette et al.[16] found that the SCFA level in the lung itself is negligible because of the lack of suitable substrates and that an increase in the SCFA level in the gut results in a detectable SCFA level in the lung. These findings indicate the possible existence of gut–lung cross talk and may explain the relief of respiratory tract symptoms in our patient. The bidirectional axis between the gut and lung compartments can be beneficial or detrimental; that is, a change in the immune response in one compartment may be associated with the immune response in the other compartment.[17,18] Hence, restoration of the gut microbiome by FMT was followed by a change in the lung, resulting in a greater immune response to opportunistic respiratory tract infections.[19] The result in this case confirms our hypothesis that FMT can be considered as an alternative treatment strategy for patients with GS.

When compared with the traditional symptomatic treatment, FMT can improve patients' quality of life by ameliorating the symptoms associated with GS and decrease medical costs because immunoglobulin replacement therapy is a never-ending and costly therapy without consistent or long-lasting effects. The patient in the present case visited our medical center because of failure of classic treatment. Her symptoms recurred despite constant use of albumin replacement therapy, the cost of which was high. Hence, FMT proved to be more cost-effective in this case; the treatment cost after FMT was reduced by half of that before FMT, both estimated over a period of 1 year. The outcome in this case was supported by our previous studies,[20] whereby FMT relieved patients' economic burden and stopped or reduced the need for use of some medications. Moreover, in the present case, the patient's psychological condition greatly improved after FMT, and she enjoyed a better state of mind and an improved appetite. The reason for this improved state of mind could have been the better control of gastrointestinal symptoms or the involvement of the microbiota in the modulation of behaviors and brain processes, including emotional behavior and ingestive behavior.[21]

Patient's perspective

"Fecal microbiota transplantation provided me with better control of symptoms, mostly the frequency of diarrhea, and improved my emotional well-being."

Conclusions

In conclusion, FMT was beneficial for a patient with GS with gastrointestinal and respiratory tract infections. Immunodeficiency, which is the culprit of GS, is impossible to cure but can be successfully managed with adequate measures. Despite the patient's immunodeficiency, the FMT did not cause any new infections, illustrating its safety. To the best of our knowledge, this is the first report of a case of GS that was successfully managed with FMT. Further studies are needed to elucidate the safety and effectiveness of FMT in patients with GS.

Abbreviations

GS: Good's syndrome, FMT: fecal microbiota transplantation; Ig, immunoglobulin, SCFA: short-chain fatty acids, GPR: G protein-coupled receptor.

Authors' contributions

S.A.J., C.L., B.C., and F.Z. contributed to the management and follow-up of the patient and the writing of the manuscript. All authors revised the manuscript and approved the final version.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report. A copy of the written consent is available for review by the editor of this journal.

Declaration of conflicting interest

Faming Zhang invented the concept of GenFMTer and transendoscopic enteral tubing and devices related to it. Sabreen Abdul Rahman Jagessar, Chuyan Long and Bota Cui declare no conflict interest.

Endnotes

GS is a complex disease characterized by hypogammaglobulinemia due to an associated

thymoma, which makes successful management difficult. FMT is a novel treatment strategy that aims to restore the gut microbiota, hence providing relief of the intestinal manifestations. The cross talk existing between compartments in the human body can provide multiple organ benefits by FMT.

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