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CASE REPORT | BILIARY

Successful Use of Fecal Microbiota Transplantation in Management of Nonobstructive Recurrent Cholangitis Following Total Pancreatectomy and Islet Autotransplant

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ABSTRACT

Alterations in the gut microbiome have been implicated in various pathologies. Fecal microbiota transplantation (FMT) has been offered as a novel treatment for conditions implicated in the disruption of the gut-microbiota axis. This case report details the successful treatment of recurrent nonobstructive cholangitis following a single FMT application in a patient who had previously undergone a hepatobiliary tract surgical diversion. Cholangitis was suspected secondary to reflux of an altered microbiome into the surgically reanastomosed biliary tract, and FMT was justified based on the history of recurrent *Clostridioides difficile* infections. This case supports the further evaluation of the utility of FMT as one potential treatment of post hepatobiliary surgical diversion cholangitis.

KEYWORDS: fecal transplant; fecal microbiota transplantation; FMT; cholangitis; total pancreatectomy islet autotransplant; pancrease; gut-microbiota axis; clostridiodes difficile; hepatobiliary; TPIAT; microbiome

INTRODUCTION

A pancreatoduodenectomy is an effective intervention in the management of severe chronic pancreatitis (CP) and involves the creation of several anastomoses, including a pancreaticojejunostomy, gastrojejunostomy, and a hepaticojejunostomy.[1] A total pancreatectomy and islet autotransplantation (TPIAT) serves as another surgical intervention to mitigate pain and improve quality of life in patients with CP refractory to medical, endoscopic, and traditional surgical management.[2] TPIAT involves the complete resection of the pancreas with partial duodenectomy, Roux-en-Y duodenojejunostomy, choledochojejunostomy, and autotransplantation of islet cells to prevent or minimize the risk of postsurgical diabetes. Recurrent episodes of cholangitis in the absence of any biliary obstruction may occur following a hepatobiliary tract surgical diversion, including in both a traditional pancreatoduodenectomy and a TPIAT.[1,3] In fact, recurrent cholangitis has been observed in 4.4% of patients with a nonstenotic hepaticojejunostomy.[4] In addition, while the fecal microbiome has been noted to be abnormal in CP, further microbiome alterations following TPIAT have also been demonstrated in one small pilot study.[5] The reflux of the altered microbiome into the biliary tract has been hypothesized as a contributing factor in postoperative nonobstructive cholangitis. Importantly, treatment of recurrent cholangitis with broad-spectrum antibiotics has the potential of increasing the pathogenic potential of commensal microbiota by favoring the selection of antibiotic-resistant bacterial strains, decreasing competitive mechanisms from nonpathogenic microbiota, and activation of the bacterial SOS response that enhances the expression of virulence factors.[6–8]

One common complication of antibiotic usage is *Clostridioides difficile* infections (CDIs), which frequently cannot be cured with antibiotics alone because of persistent dysbiosis in the gut and failure to eradicate *C. difficile* spores.[9] Fecal microbiota transplantation (FMT), which involves the delivery of fecal microbiota from healthy donors, has emerged as a highly effective therapeutic strategy in managing recurrent CDI.[9,10] There is a growing interest in using microbial therapeutics, including FMT, in a variety of non-CDI

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indications, including lowering the burden of antimicrobial resistance and virulence factors of the gut microbiota. This case demonstrates the potential use of FMT in the management of nonobstructive recurrent cholangitis in a post-TPIAT patient.

CASE REPORT

A 51-year-old White woman, status post-TPIAT in 2011 for recurrent pancreatitis associated with pancreas divisum, was referred to our institution in 2021 because of recurrent episodes of sepsis suspected secondary to cholangitis occurring at progressively shorter intervals, further complicated by recurrent CDI. Her medical and surgical history were notable for post-surgical insulin-dependent diabetes mellitus and status post-Roux-en-Y lateral pancreaticojejunostomy procedure (Puestow procedure) along with cholecystectomy, partial gastrectomy, and splenectomy in 2007.

She experienced 5 hospitalizations over 2 years for sepsis, presenting acutely with high fevers, shaking chills, abdominal pain, increased inflammatory markers (C-reactive protein and white blood cell count), and mildly elevated liver function tests, most consistent with cholangitis. Magnetic resonance cholangiopancreatography consistently excluded biliary obstruction. The patient was managed with rotating broad-spectrum intravenous antibiotics (ertapenem, levofloxacin, piperacillin/tazobactam, metronidazole, and vancomycin). Her course was further complicated by bacteremia with extended spectrum beta-lactamase-positive *Escherichia coli,* chronic carriage of enteropathogenic *E. coli*, and 6 episodes of CDI confirmed by polymerase chain reaction and *C. difficile* toxin enzyme immunoassay assays. The CDI episodes were treated with repeated courses of oral vancomycin and rifaximin. The serial hospitalizations severely affected her quality of life.

The patient was offered fecal microbiota transplantation (FMT) to terminate the cycle of CDI recurrence but also with the hope that the engraftment of healthy donor microbiota would lessen the pathogenicity of her microbiome. Therefore, the donor microbiota was delivered simultaneously through upper endoscopy and colonoscopy into the jejunum and colon, respectively. Specifically, each site received compound MTP-101LR (1.3×10^{12} bacteria per unit), a cryopreserved liquid suspension of healthy donor microbiota prepared by the University of Minnesota Microbiota Therapeutics Program.[11] The patient has since been followed for 30 months and has not developed further bouts of CDI or cholangitis requiring antibiotics, suggesting the persistence of FMT benefit (Figure 1).

DISCUSSION

Anatomic and functional disruption in the gastrointestinal tract during and after TPIAT, periodic exposure to broad spectrum antibiotics and enteral nutrition, and fluctuations in the use of opioid and other pain medications have been demonstrated to cause post-TPIAT dysbiosis.[5] Our patient's refractory cholangitis infection likely emanated from her surgically altered anatomy following her pancreatectomy, with a blind biliary limb now outside the enteral stream, which may have facilitated bacterial overgrowth as one contributor to the gut dysbiosis, and her newfound anastomoses sites, which may have enabled bacterial gut translocation.[12] In addition, the microbiota adapted to severe antibiotic pressure, termed "pathobiome" has greater potential for pathogenicity due to higher expression of virulence factors and loss of microbiota-derived factors that strengthen the gut barrier function.[8,13] While FMT is a well-established treatment in the management of refractory and recurrent *C. difficile* infections, antibiotic management is still the only available medical therapy in the management of cholangitis. This patient experienced repeated failures of antibiotic management with multiple hospitalizations, and thus, FMT was considered as an alternate strategy to restructure the patient's microbiome for symptom alleviation and potential resolution of pathologies related to gut dysbiosis.[14,15] Unlike antibiotic treatment of gut dysbiosis, FMT can transplant a diverse and more complete fecal microbial community of organisms to rebalance the gut-microbe axis and decrease the burden of antimicrobial resistance genes and virulence factors.[13,16,17] Future prospective studies of FMT as a treatment of recurrent cholangitis in this population should be considered.

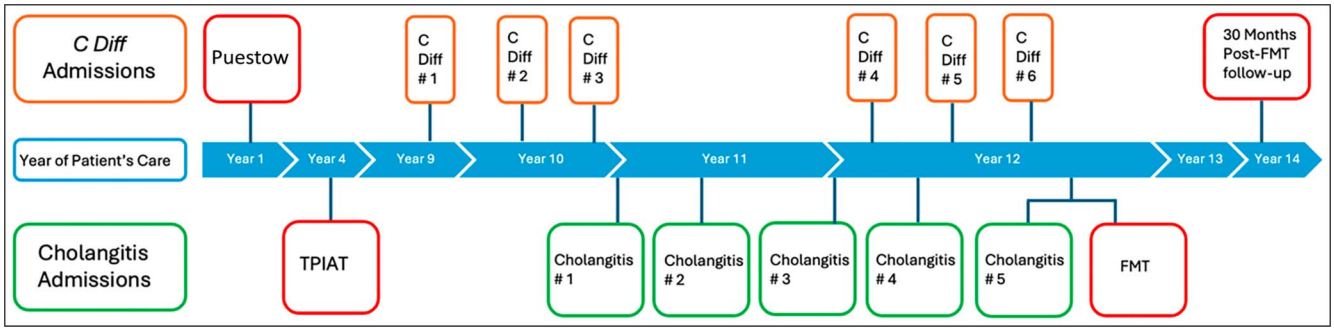

Figure 1. Patient's cholangitis and FMT treatment timeline. Year one denoted in Patient's care with their Puestow intervention for chronic pancreatitis. Admissions related to *C. Difficile* and cholangitis are indicated through years 9–12. Timeline end point indicated at 30 months post-FMT follow-up, with no subsequent *C. Difficile* or cholangitis infections following FMT. *C. Difficile, Clostridioides difficile*; FMT, fecal microbiota transplantation.

In addition, with further investigation, FMT may be able to serve as a reasonable treatment option for patients with non-obstructive cholangitis suspected to originate from gut dysbiosis in a postoperative setting of procedures with afferent limbs including a Roux-en-y and choledochojejunostomy or hepaticojejunostomy, regardless of the original indication for the initial surgery (stricture, neoplasms). The narrative presented here, represents one case to support the continued investigation and benefit of FMT as a viable intervention to reconstruct a dysregulated gut-microbe axis and further expands its potential indications.

DISCLOSURES

Author contributions: A. Scott took the lead in writing the manuscript. All authors contributed to the care of the patient and conception of treatment plan. All Authors contributed to the interpretation of the case study. All authors provided critical feedback and helped shape the research, analysis and manuscript. G. Trikudanathan is the article guarantor.

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