CASE REPORT

Available from: http://www.jgld.ro/wp/archive/y2016/n3/a20
DOI: http://dx.doi.org/10.15403/jgld.2014.1121.253.cel

Serendipity in Refractory Celiac Disease: Full Recovery of Duodenal Villi and Clinical Symptoms after Fecal Microbiota Transfer

Yvette H. van Beurden[1,2], Tom van Gils[1], Nienke A. van Gils[3], Zain Kassam[4,5], Chris J.J. Mulder[1], Nieves Aparicio-Pagés[3]

1) Dept. of Gastroenterology & Hepatology, and
2) Dept. of Medical Microbiology & Infection Control, VU University Medical Center, Amsterdam, The Netherlands
3) Dept. of Gastroenterology & Hepatology, Canisius Wilhelmina Ziekenhuis, Nijmegen, The Netherlands
4) Massachusetts Institute of Technology, Cambridge, Massachusetts, USA;
5) OpenBiome, Medford, Massachusetts, USA.

Address for correspondence:
Y.H. van Beurden, MD
Dept. of Gastroenterology & Hepatology
De Boelelaan 1118, PK 2X 132
1081 HZ Amsterdam
The Netherlands
y.vanbeurden@vumc.nl

Received: 10.05.2016
Accepted: 10.06.2016

ABSTRACT

Treatment of refractory celiac disease type II (RCD II) and preventing the development of an enteropathy associated T-cell lymphoma in these patients is still difficult. In this case report, we describe a patient with RCD II who received fecal microbiota transfer as treatment for a recurrent *Clostridium difficile* infection, and remarkably showed a full recovery of duodenal villi and disappearance of celiac symptoms. This case suggests that altering the gut microbiota may hold promise in improving the clinical and histological consequences of celiac disease and/or RCD II.

Key words: refractory celiac disease type II – *Clostridium difficile* infection – fecal microbiota transplantation

Abbreviations: CDI: *Clostridium difficile* infection; EATL : enteropathy associated T-cell lymphoma; FMT: fecal microbiota transfer; IEL: intraepithelial lymphocytes; RCD II: refractory celiac disease type II; TPN: total parenteral nutrition.

INTRODUCTION

A small minority of patients with celiac disease develop refractory celiac disease type II (RCD II). This is a rare autoimmune condition defined by a persistent malabsorptive state, villous atrophy, and more than 20% of intraepithelial lymphocytes (IEL) with an aberrant phenotype (surface CD3-, intracellular CD3+) despite adherence to a full gluten free diet [1]. Current treatment consists of non-slow release budesonide, cladribine (a synthetic purine nucleoside homologue), and autologous stem cell transplantation. However, the prognosis is poor, with a five-year mortality of about 55% [1]. Complications of RCD II include progressive malabsorption and an enteropathy associated T-cell lymphoma (EATL).

Fecal microbiota transfer (FMT) is an effective therapy for recurrent *Clostridium difficile* infection (CDI) [2], and has shown promise in the treatment of autoimmune conditions, such as inflammatory bowel disease [3], where the microbiome may be implicated in the disease pathology. Here, we present an unexpected promising outcome of a case of RCD II after treatment with FMT for CDI.

CASE PRESENTATION

A 68-year old woman with RCD II was admitted to the hospital because of severe diarrhea, dehydration, and malnutrition (body mass index, BMI, 17.3 kg/m^2).

Medical history revealed RCD II for over 10 years (villous atrophy, and >80% aberrant cells). Except for a strict gluten free diet, the patient had refused treatment because of manageable symptoms until two years prior to admission, when additional treatment with budesonide (9 mg per day) was initiated.

Evaluation of the diarrhea included duodenoscopy and stool tests for *C. difficile, Campylobacter, Salmonella, Yersinia, Shigella, Giardia, Dientamoeba fragilis*, and *Cryptosporidium*. Duodenal biopsies showed villous atrophy (Marsh IIIA). The stool test was positive for *Cryptosporidium*. The patient was treated with paromomycin for *Cryptosporidium*, and budesonide was continued for RCD II. Since RCD II should be considered as a low-grade lymphoma, a PET-CT was performed to rule out EATL proving negative. The patient's hospital admission was complicated by a hospital-acquired pneumonia, which was treated with a seven-day course

of ceftriaxone 2000mg intravenously. After a month of hospitalization the patient was discharged.

One month after discharge, the patient was readmitted because of severe diarrhea (>10 unformed bowel moments, UBM, per day) and dehydration. Her BMI had further decreased to 15.5 kg/m^2. Total parenteral nutrition (TPN) and albumin supplementation was initiated. Again, microbiological workup and duodenoscopy were performed. Detailed analysis of the biopsy samples using flow cytometry showed the presence of aberrant lymphocytes (87% of total intra-epithelial lymphocytes, IELs). Stool tests did not reveal any enteropathogen. Unfortunately, the patient experienced a second hospital acquired pneumonia as well as central line sepsis, and was treated with a five-day course of ceftriaxone 2000mg intravenously, and a 14-day course of flucloxacillin 500mg orally TID. After successful treatment of these infections, the patient admitted to receive a five-day course of cladribine as an additional treatment for RCD II, after which she was discharged. Since cladribine may suppress bone-marrow function, prophylaxis with cotrimoxazole (480mg daily) and valaciclovir (500mg BID) was indicated for the following twelve months.

The patient was readmitted again within three weeks, because of severe diarrhea, and electrolyte disturbance on a background of ongoing budesonide and TPN. Initially, intravenous methylprednisolone was started; however, because of the development of a third hospital-acquired pneumonia, treated with ceftriaxone, methylprednisolone was stopped. Two weeks after successful treatment of the pneumonia, toxigenic culture was positive for *C. difficile*. This first episode of CDI was treated with a 10-day course of vancomycin (250mg orally QID); the subsequent recurrence of CDI within three weeks with a tapered vancomycin regimen for 38 days. The patient was discharged one week after diagnosis of the CDI recurrence. After the tapered therapy, stool culture for *C. difficile* was negative, and the patient was admitted to the hospital for five days to receive a second five-day course of cladribine for RCD II treatment.

Two months later, the patient developed a third episode of CDI, which was treated with FMT via nasoduodenal tube. The FMT material was obtained from a healthy, rigorously screened donor from OpenBiome, an international public stool bank (donor age: 22 years old, sex: male, BMI: 23.1 kg/m^2, waist circumference: 31.6 inches). Duodenal biopsies, obtained before placement of the nasoduodenal tube, still showed villous atrophy (Marsh IIIA). Although the patient developed fever, with increased inflammation parameters (C-reactive protein 208 mg/L; leucocytes 31.5x10^9/L) within the first four days after FMT, the diarrhea decreased dramatically to three formed stools per day within two weeks. One month after FMT, the patient was discharged. At one-month follow-up, evaluation of post-FMT duodenal biopsies showed persistent villous atrophy and the presence of aberrant cells (78%). However, the patient gained weight and had no symptoms of diarrhea. Remarkably, duodenal biopsies obtained six months after FMT showed complete recovery of the villous atrophy (Marsh 0). Aberrant cells were still present (71%), which is seen more often in clinically and histologically improved RCD II patients. Clinically, her BMI had increased to 20.5 kg/m^2. Besides maintaining a gluten free diet, treatment for RCD II has been stopped with ongoing quiescent disease. Clinically, the patient is totally free of celiac symptoms (Fig.1).

A stool sample from the donor was assessed by high-throughput 16S rRNA microbiome sequencing using an Ilumina MiSeq. The donor was observed to have a Shannon Diversity Index of 3.81, higher than the mean (3.26) or median (3.36) observed across 29 other FMT donors from the international public stool bank (Fig. 2). Unfortunately, we had no baseline fecal sample of the patient before FMT, which made it impossible to investigate microbial dynamics of the patient over time, or compare microbial composition of the donor with that of the patient.

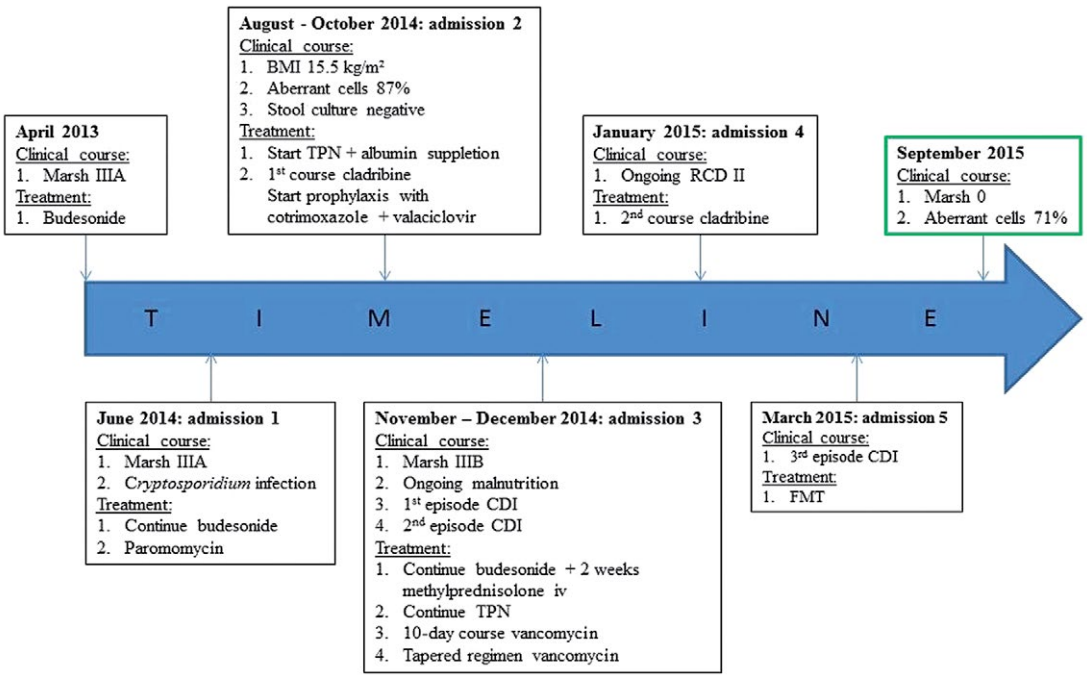

Fig. 1. Summary of clinical course. TPN: total parenteral nutrition CDI: *Clostridium difficile* infection FMT: fecal microbiota transfer.

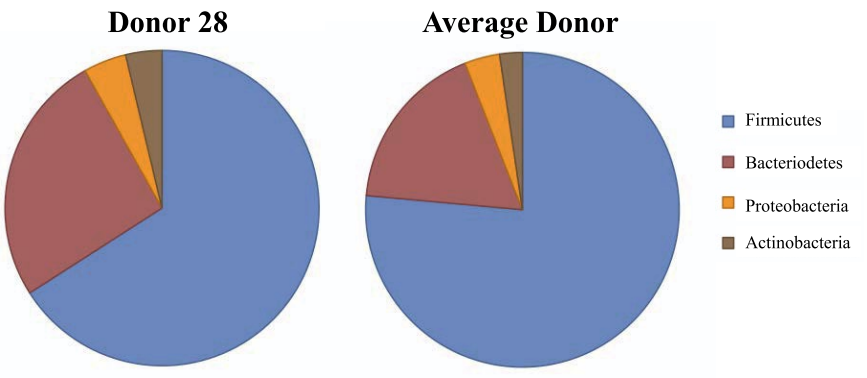

Fig. 2. The phylum-level composition of donor 28 (used for fecal microbiota transfer in this patient) relative to the average of the 29 healthy donors of the international public stool bank.

DISCUSSION

It is unknown whether development of RCD II is caused by any of the known genetic risk factors for celiac disease, the immunologic factors, the environmental factors, or their combination [1, 4]. There might be a role for the anti-apoptotic effect of IL-15, and natural killer group 2 member D (NKG2D) ligand expression on intestinal epithelial cells in (refractory) celiac disease [1, 5]. Among environmental factors, intestinal microbiota has been implicated in celiac disease. It is suggested that dysbiosis functions as a driver for the IL-15 cytokine response and IEL activation, and that the microbiome plays an essential role in the development of the mucosal immune system [6]. Several studies on fecal samples and duodenal biopsies of celiac disease patients suggest that an imbalanced microbiota in these patients could have a pathogenic role in inducing modification of the mucosal barrier which maintains persistent immune activation, causing clinical symptoms [7]. Thereby, it was suggested that the constitutive levels of the NKG2D ligand expression on intestinal epithelial cells are also regulated by microbial signalling in the gut [8]. Despite these data regarding the role of patient's intestinal microbes in clinical symptoms and manifestation of celiac disease and RCD II, to our knowledge, manipulation of the microbiota to mitigate the pathophysiology of celiac disease and/or RCD II has not previously been performed or discussed.

In recent years, several types of treatment for RCD II have been suggested [1]. Preventing an EATL, and eliminating clinical symptoms is the goal of therapy in RCD II. Cladribine, a synthetic purine nucleoside homologue, is supposed to be especially effective against low-grade malignancies, however, our patient did not respond to cladribine therapy, since diarrhea (> 10 UBM per day) and malnutrition persisted, and duodenal biopsies showed no reduction of aberrant cells and villous atrophy four months after the second course of cladribine. By serendipity we discovered that FMT, commonly used for CDI in recent years, might be of benefit for RCD II.

CONCLUSION

This case suggests that altering the gut microbiota may hold promise in improving the clinical and histological consequences of celiac disease and/or RCD II. It is tempting to speculate that altering the composition of the microbiota could also help restore villous atrophy. This novel treatment modality should be further investigated, particularly among patients failing to respond to cladribine treatment before performing an autologous stem cell transplantation.

Conflicts of interest: Zain Kassam is employed at OpenBiome, a nonprofit stool bank that provides clinicians with preparations for fecal microbiota transfer and supports research into the microbiome.

Authors' contributions: Y.B. performed FMT, collected data, drafted the case report. T.G. collected, and interpreted data about patient's medical history and RCD II diagnosis, and revised the manuscript. N.G. collected and provided data about the hospital admissions. Z.K. provided general information about the feces donor, and extensively reviewed the manuscript. C.M. was responsible for the patient during FMT and extensively reviewed the manuscript. M.A.P. was responsible for the patient during different hospital admissions.

REFERENCE

1. van Gils T, Nijeboer P, van Wanrooij RL, Bouma G, Mulder CJ. Mechanisms and management of refractory coeliac disease. Nat Rev Gastroenterol Hepatol 2015; 12: 572-579. doi: 10.1038/nrgastro.2015.155
2. van Nood E, Vrieze A, Nieuwdorp M, et al. Duodenal infusion of donor feces for recurrent Clostridium difficile. N Engl J Med 2013; 368: 407-415. doi: 10.1056/NEJMoa1205037
3. Moayyedi P, Surette MG, Kim PT, et al. Fecal microbiota transplantation induces remission in patients with active ulcerative colitis in a randomized controlled trial. Gastroenterology 2015; 149: 102-109. doi: 10.1053/j.gastro.2015.04.001
4. Wacklin P, Kaukinen K, Tuovinen E, et al. The duodenal microbiota composition of adult celiac disease patients is associated with the clinical manifestation of the disease. Inflamm Bowel Dis 2013; 19: 934-941. doi: 10.1097/MIB.0b013e31828029a9
5. Mention JJ, Ben Ahmed M, Begue B, et al. Interleukin 15: a key to disrupted intraepithelial lymphocyte homeostasis and lymphomagenesis in celiac disease. Gastroenterology 2003; 125: 730-745. doi: 10.1016/S0016-5085(03)01047-3
6. Kim SM, Mayassi T, Jabri B. Innate immunity: actuating the gears of celiac disease pathogenesis. Best Pract Res Clin Gastroenterol 2015; 29: 425-435. doi: 10.1016/j.bpg.2015.05.001

7. Marasco G, Di Biase A, Schiumerini R, et al. Gut microbiota and celiac disease. Dig Dis Sci 2016; 61: 1461-1472. doi: 10.1007/s10620-015-4020-2

8. Hansen CH, Holm TL, Krych L, et al. Gut microbiota regulates NKG2D ligand expression on intestinal epithelial cells. Eur J Immunol 2013; 43: 447-457. doi: 10.1002/eji.201242462

Șansa pentru boala celiacă refractară: refacerea completă a vilozităților duodenale și dispariția simptomelor clinice după transferul de microbiom fecal

ABSTRACT / REZUMAT

Tratamentul bolii celiace refractare tip II (RCD II) și prevenirea dezvoltării unei enteropatii associate cu limfomul cu celule T la acești pacienți este dificil. În această observație clinică, prezentăm un pacient cu RCD II care a primit un transplant fecal pentru tratamentul unei infecții refractare cu *Clostridium difficile* și, surprinzător, a prezentat completa refacere a vilozităților duodenale și dispariția simptomelor bolii.