Disease remission after commencing naltrexone in an atypical case of Crohn’s disease complicated by recurrent Clostridium difficile infection

Afrasyab Khan, John Perry

ABSTRACT

Introduction: Crohn’s disease (CD) is typically a chronic relapsing condition of the gastrointestinal tract. Granulomas can be present which are typically non-necrotizing. CD can be triggered as well as complicated by gastrointestinal infections. We present an atypical case of Crohn’s disease with necrotizing granulomas that was triggered by Clostridium difficile infection (CDI). Case Report: A 40 years woman presented with chronic diarrhoea and investigations showed CDI. With no sustained response to metronidazole and vancomycin she came forward for a colonoscopy which showed features of Crohn’s disease. This was confirmed on histology. After a period of remission on adalimumab she required a right hemicolectomy for a severe flare. The resection specimens showed necrotizing granulomas. No alternative cause for necrotizing granulomas was found. The patient had recurrent CDI during follow-up requiring faecal microbial transplant resulting in symptom resolution. Since the patient declined the traditional immunosuppressive medications used in CD due to recurrent upper respiratory tract infections, we commenced her on oral naltrexone. She has currently been in complete remission for 30 months with low dose naltrexone. Initial diagnosis was made difficult and then revisited due to infectious gastroenteritis, recurrent diclofenac use and extra-intestinal manifestations. Conclusion: CD triggered by infectious gastroenteritis and other confounders can make the diagnosis challenging. Necrotizing granulomas - though uncommon - can be present in CD. Recurrent CDI is known to be more common in CD and could act a trigger of CD flares. Low dose naltrexone may be used as a potential treatment for CD in selected cases.

Keywords: Clostridium difficile, Crohn’s Disease, Faecal microbial transplant, Naltrexone, Necrotizing granulomas

INTRODUCTION

Crohn’s disease is a chronic relapsing inflammatory disorder of the gastrointestinal system of unknown aetiology with extra-intestinal manifestations. It results from an altered immune response to an as yet unidentified luminal antigen or microorganism in a genetically susceptible person often with an environmental trigger [1, 2]. It frequently occurs after infectious gastroenteritis [3]. Patients with inflammatory bowel disease (IBD)
are known to be more susceptible to gastrointestinal infections especially Clostridium difficile infection (CDI). New Zealand has one of the highest incidences of IBD in the world and a striking increase in this has been noted in the last several decades [4–9]. We present an atypical case of Crohn’s disease with necrotizing granulomas. The patient also had recurrent CDI needing faecal microbial transplant (FMT).

CASE REPORT

A 40-year-old woman who initially presented late 2011 with 6 weeks of diarrhoea. A close contact has had a similar acute but in his case it was a self-limiting presentation on returning from Samoa. Although stool cultures had been negative, she was treated with two courses of antibiotics without benefit in the community. Her past history was of vitiligo, mild asthma and osteoarthritis. There was no family history of inflammatory bowel disease. She was taking diclofenac 75mg once a day for osteoarthritis. A colonoscopy was performed and showed multiple small ulcers in the terminal ileum and throughout the colon. Histology was consistent with non-specific acute inflammation. Histology did not show any features of inflammatory bowel disease.

Stool specimens had been negative for infections but repeat testing returned positive for Clostridium difficile toxin so the ulceration was presumed due to this and the diclofenac she had been taking. She was advised to stop the diclofenac. She was given a course of metronidazole for CDI however there was no response. Following this she only had a partial response to a course of vancomycin. She was eventually started on 40mg of prednisone (tapering the dose weekly) which also only gave a partial response and could only be tapered to 20mg initially.

A repeat colonoscopy was done at this stage and now the findings were consistent with Crohn’s disease. There was moderate inflammation and ulceration in the terminal ileum. Biopsies showed chronic inflammation and one small granuloma. The colon was now macroscopically normal but on histology microscopic inflammation was noted throughout the colon but not rectum. Gastroscope did not show any evidence of upper gastrointestinal tract involvement with normal biopsies and negative duodenal aspirate for parasites. MRI (magnetic resonance imaging) enterography showed 25 cm of distal ileal inflammation without focal stricturing. No other areas of small bowel involvement were identified. The working diagnosis at this point was Crohn’s disease triggered by initial CDI.

Azathioprine was trailed but not tolerated due to a typical hypersensitivity reaction. Methotrexate caused significant fatigue and severe alopecia so this was also discontinued. Adalimumab monotherapy was started after pre-biologic screening tests including Quantiferon gold (which was negative). Remission was eventually achieved which lasted for about nine months. She developed recurrent CDI and another flare of her Crohn’s disease, eventually settling with steroids, vancomycin and reloading of the adalimumab. It transpired she had also been taking over the counter NSAIDs before this flare of disease, since she was a keen runner but with osteoarthritis. These were stopped. She continued to be in remission on adalimumab monotherapy for the next 15 months until a further flare with extra-intestinal manifestations of uveitis, polyarthritis and a significant knee effusion. A knee aspirate ruled out any infection or crystal arthropathy. A repeat colonoscopy showed severe ulceration in the right colon, but a virtually normal ileum (Figure 1).

There was no response to intravenous steroids and reloading of adalimumab hence she came forward for a right hemicolecetomy having exhausted all the funded options available. The resection specimen of the colon...
had necrotizing granulomas Figure 2(A–D). There was no evidence of vasculitis on histology. As necrotizing granulomas are more in keeping with an infective aetiology, we investigated thoroughly for an alternative diagnosis with no positive finding. These included acid fast bacilli (AFB) stains, tuberculosis (TB) and 16S ribosomal PCRs on the colonic specimens, Quantiferon gold, DNA sequencing for mycoplasma heat shock proteins, serum angiotensin converting enzyme (ACE), Yersinia and Treponemal serology. There was no history of exposure to farm animals. A computed tomography (CT) scan of her chest and abdomen did not show any evidence of sarcoidosis or malignancy. As she previously had uveitis and multiple oral ulcerations a diagnosis of Behcets disease was considered. Multiple autoimmune and vasculitis screens were negative including anti-nuclear antibody, anti-neutrophil cytoplasmic antibody, anti-Saccharomyces cerevisiae antibody and extractable nuclear antigens. HLAB51 was negative. Immunoglobulins levels were normal and she did not meet criteria for combined variable immunodeficiency. Post operatively oral steroids were weaned off. The patient declined any further immunosuppression including any biologics due to previous recurrent upper respiratory tract infections. Hence she remained off immunosuppression and was followed closely.

During follow-up, repeat stool samples were once again positive for C. difficile toxin (with a few negatives as well) so it was hypothesized that recurrent CDI might be exacerbating her Crohn’s disease. Hence the decision was made to take CDI out of the picture and she came forward for faecal microbial transplant (FMT) via colonoscopy. FMT with the first donor resulted in complete dramatic remission with the first solid stools in many months, but she relapsed 5 days later. Three further FMTs were done and treatment with a third donor finally gave lasting control of her diarrhoea. She has had another flare of Crohn’s after FMT but with no diarrhoea this time. With no other funded options she was started on low-dose oral naltrexone 4.5mg daily for Crohn’s disease. Her C-reactive protein normalized and faecal calprotectin was almost normal during follow-up. Since starting naltrexone Miss G has been in complete remission for the past 30 months.

**DISCUSSION**

Crohn’s disease is a chronic relapsing inflammatory disorder of the gastrointestinal system of unknown aetiology with extra-intestinal manifestations. It results from an altered immune response to an as yet unidentified luminal antigen or microorganism in a genetically susceptible person often with an environmental trigger [1, 2]. CD can be triggered after infectious gastroenteritis [3]. In this case the Crohn’s disease was likely triggered by the initial infection that the close contact had as well. The patient was initially treated for CDI but did not have complete response likely due to underlying Crohn’s disease which became evident later on.

Colonoscopy with ileoscopy and biopsies is the most widely used modality to aid in the diagnosis [10]. In patients with CD, non-caseating granulomas can be detected in up to 60% of bowel specimens on histology after resection, however they are only present in up to 36% biopsy specimens obtained during endoscopy [11]. Necrotizing granulomas are not unknown in Crohn’s disease but are rare [12]. The cause of necrotizing granulomas is commonly infective. Other causes including vasculitis like granulomatosis with polyangiitis (GPA) can also result in necrotizing granulomas [13]. The combination of intestinal inflammation and extra-intestinal manifestations mainly aphthous ulceration and uveitis makes Behcet’s disease a differential. Behcet’s disease is a chronic inflammatory disorder with multisystem vasculitis [14]. The patient had extensive investigations for possible infection or vasculitis without any positive findings. This patient did not meet criteria for diagnosis of Behcet’s disease and there was no vasculitis on intestinal biopsies.

Alteration in gastrointestinal microbiota or dysbiosis has been linked to several gastrointestinal conditions including Crohn’s disease [15]. There is increasing evidence that inflammatory bowel disease results from altered immune response to luminal antigens or microbes [1, 2]. Dysbiosis from gastrointestinal infection in this patient could have predisposed her to the development of Crohn’s disease as well as increased susceptibility to CDI [16]. The severity of Crohn’s disease, abscess formation and need for operative intervention at a younger age may also be related to dysbiosis [17, 18]. Intestinal dysbiosis increases susceptibility to Clostridium difficile infection(CDI); and this occurs most commonly after the use of antibiotics [16].

*Clostridium difficile* causes disease ranging from a mild diarrhoea to severe life-threatening colitis with incidence of this infection increasing in recent years both in the community and in-hospital [19, 20]. CDI occurs most often in patients with IBD compared to the general population and mostly manifests as a more severe disease with a higher rate of complications [21]. This patient had a very difficult to eradicate recurrent CDI likely triggering flares of CD. The natural immune response to CDI is altered in patients with IBD due to decreased barrier function of the gastrointestinal tract and immunosuppression due to treatment with steroids and immunomodulators [22]. Dysbiosis often resulting from antibiotic treatment predisposes to CDI as flora that normally keeps clostridium difficile in check is disrupted. *Clostridium difficile* spores are mostly resistant to antibiotics. After treatment of CDI the residual flora in the bowel may not be able to out-compete C. difficile germinating from spores resulting in recurrent CDI [23]. After one recurrence, up to 65% patients have subsequent recurrences once treatment is stopped [24]. There is a
significant risk of relapse with pulsed or tapered antibiotic regimens as well [24].

FMT is considered for patients with recurrent CDI especially in case of a third recurrence and previous treatment with a pulsed or tapered regimen. It can be delivered via nasogastric or nasojejunal tubes, enemas or via colonoscopy. By 2011 almost 75% of FMT worldwide were done via colonoscopy. The results are significantly better than vancomycin alone with 91% primary and 98% secondary cure rate [25]. The patient in this case needed several treatments to achieve complete remission.

Our patient has been in remission on naltrexone which is not a traditional medication for maintaining remission in IBD. Naltrexone is an opioid receptor antagonist. Opioid receptors are present on intestinal as well as peripheral immune cells that regulate inflammation. Activation of these receptors sensitize T-cells and macrophages to pro-inflammatory stimuli [26]. Naltrexone has been shown to result in a significant decrease in CDAI (Crohn’s disease activity index) as well as CDEIS (Crohn’s disease endoscopy index severity score) compared with placebo [27].

CONCLUSION

In nutshell, this is a case of typical Crohn’s disease triggered by and on-going flares likely due to recurrent CDI. Initial diagnosis was challenging and then revisited due to infectious gastroenteritis, recurrent diclofenac use, necrotizing granulomas and extra-intestinal manifestations. Recurrent CDI was successfully treated with FMT and the patient continues to be in remission currently from Crohn’s disease with low dose naltrexone.

REFERENCES


Author Contributions
Afrasyab Khan – Acquisition of data, Analysis and interpretation of data, Drafting of the article, Revising it critically for important intellectual content, Final approval of the version to be published
John Perry – Substantial contributions to conception and design, Analysis and interpretation of data, Drafting of the article, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor of Submission
The corresponding author is the guarantor of submission.

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Consent Statement
Written informed consent was obtained from the patient for publication of this case report.

Conflict of Interest
Authors declare no conflict of interest.

Data Availability
All relevant data are within the paper and its Supporting Information files.

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