CASE REPORTS

A case of intestinal Behcet's disease under Adalimumab

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ABSTRACT

Behcet's disease (BD) is a multisystem mucocutaneous inflammatory condition characterized by recurrent genital and oral ulcers, ocular inflammation, and can involve the gastrointestinal tract. Treatment involves the usage of immunosuppressive agents to control the disease with glucocorticoids utilized for treatment of flares. Tumor necrosis factor inhibitors are frequently used to control the disease as well. We present the case of a 40 years old African American female presenting with intestinal BD that was refractory to adalimumab therapy. In conjunction with glucocorticoids, the patient's intestinal disease was controlled with infliximab therapy. Currently, there have been no studies comparing the efficacy of TNFα inhibitors on the treatment of BD. Future studies are needed to compare the efficacy of TNFα inhibitor agents in the treatment of intestinal manifestations of BD.

Key Words: Behcet's disease, Gastrointestinal inflammation, Colonic ulcers, Tumor necrosis factor inhibitors

1. INTRODUCTION

Behcet's disease (BD) is a multisystem mucocutaneous inflammatory condition that is characterized by recurrent genital and oral ulcers, ocular inflammation, and has the capacity to involve the gastrointestinal tract. BD is most common in native populations of Eurasia and East Asia while gastrointestinal manifestations of BD are more prevalent among East Asian populations.[1,2] Anti-TNF (Anti-tumor necrosis factor) agents are increasingly being used for severe manifestations of BD.[3]

2. CASE PRESENTATION

A 40 years old African-American female was diagnosed with BD five years prior to presentation with a history of recurrent large, painful genital ulcers that demonstrate neutrophilic dermatoses on biopsy. She had been treated with prednisone and cyclosporine in the past and was transitioned to azathioprine for refractory hypertension. Two years prior to the presentation, adalimumab 40 mg weekly was added to her regimen because of recurrent oral and genito-anal ulcers. Her disease had improved with this latter regimen, with rarer oral ulcers and less than 2 genito-anal ulcers per year. She reported compliance with this regimen and had no difficulties with medication administration.

She initially presented to outpatient Rheumatology with a one week history of persistent fevers, intermittent severe periumbilical abdominal pain, and non-bloody diarrhea. She denied hematochezia or melena. She never complained of gastrointestinal symptoms with her prior flares which included fevers and oral ulcers. Given new abdominal pain, fevers, and diarrhea in the setting of her immunosuppressive

therapy, the patient was admitted for inpatient workup.

On admission, the patient was febrile to 39.4°C and tachycardic to 120 s. The patient's physical examination was significant for right lower quadrant abdominal tenderness with rebound tenderness and four oral ulcerative lesions. Admission blood count was significant for a leukocytosis of 10,500/μl with a differential notable for 12.7% band neutrophils. Blood cultures were negative. Inflammatory markers were elevated with a C-reactive protein and erythrocyte sedimentation rate at 20 mg/dl (normal: 0-0.49 mg/dl) and 120 mm/hr, respectively. Stool studies were negative for infectious cultures, leukocytes, Clostridium difficile toxin, rotavirus, or cytomegalovirus (CMV). Serum quantitative DNA for CMV was negative. A CT of her abdomen and pelvis with IV contrast was negative for evidence of infectious or inflammatory bowel disease.

Figure 1. Colonscopic imaging revealing cecal ulceration and ileocecal valve stenosis
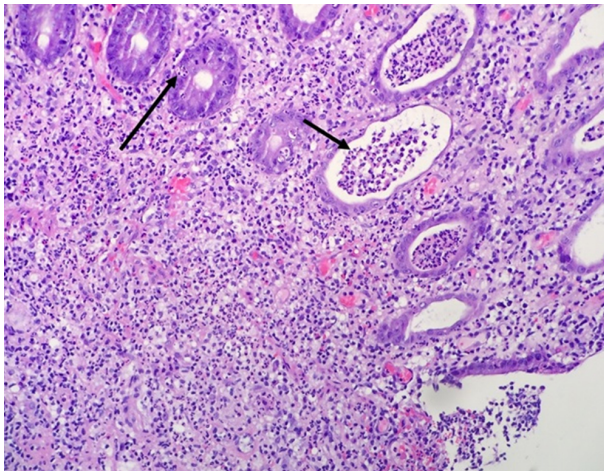
Figure 2. Cecal mucosal biopsy demonstrating active inflammation with cryptitis (long arrow) and crypt abscesses (short arrow). Neutrophils are present in the submucosal and lamina propria. There is no histologic evidence of vasculitis.

The patient underwent esophagoduodenoscopy (EGD) and colonoscopy. The EGD was normal without evidence of upper GI involvement. Rectal examination was significant for multiple anal ulcerations. Colonoscopy revealed circumferential ulceration and thickening of the ileocecal valve with high grade stenosis (see Figure 1). There were scattered ulcerations (5-10 mm diameter) in the ascending and transverse colon. The terminal ileum was notable for two ulcers with otherwise normal appearing mucosa. Multiple biopsies were taken which showed inflammation with cryptitis and crypt abscesses in the cecum with no definitive histologic evidence of vasculitis (see Figure 2). Distal colonic biopsies demonstrated patchy active colitis with cryptitis and crypt abscesses. Neutrophils were notable in the lamina propria (see Figure 2).

Figure 3. Ileocecal valve during follow up colonoscopy performed 10 months following initial presentation for gastrointestinal manifestations of BD. There were no ulcerations present, and the stenosis of her ileocecal valve had resolved.

The patient was initiated on oral prednisone 40 mg daily with a tapering dose and infliximab at 5 mg/kg. Adalimumab was discontinued. Three months after an initial response, the patient had intermittent abdominal pain with non-bloody diarrhea and thus her oral prednisone was re-initiated to 60 mg taper and her infliximab dose was increased to 10 mg/kg. Following this dose adjustment, the patient's symptoms were controlled, and she returned to normal bowel movements. After tapering prednisone therapy, repeated colonoscopy was performed 10 months following her initial presentation demonstrated normal mucosa without ulceration with normal histology. The stenosis of her ileocecal valve had resolved (see Figure 3).

3. DISCUSSION

This clinical vignette represents a case of BD with gastrointestinal manifestations of BD presented while on treatment with adalimumab. Intestinal BD was only controlled with oral glucocorticoids and a switch to infliximab, at high dose, an alternative TNF-α inhibitor. There has only been one

other case report in the literature describing the incidence of intestinal manifestations while on adalimumab therapy.[4]

Gastrointestinal manifestations of BD are associated with significant morbidity and mortality in patients. The most common presenting symptoms are abdominal pain, nausea, vomiting, and gastrointestinal bleeding.[1] Intestinal involvement of BD usually appears within 4-6 years following the onset of oral ulcerative lesions.[5] Overall, BD can present at any location in the gastrointestinal tract. However, it has a predilection for ileocecal involvement.[1] Endoscopic evaluation demonstrates characteristic findings of which can be discrete lesions, large (> 1 cm), and single to few in number.[1] Presence of typical lesions with systemic BD has been shown to be 100% specific for intestinal BD based on diagnostic criteria proposed by Cheon et al.[2]

Treatment of intestinal BD is similar to that of inflammatory bowel diseases. Sulfasalazine and 5-aminosalicyclic acid have been the mainstay of therapy.[1] Treatment in the acute setting of intestinal BD flares is primarily corticosteroid therapy with additional steroid sparing medications such as azathioprine.[4] Since the advent of TNFα inhibitor therapy, these medications have been used to control moderate to severe intestinal BD.[1] Adalimumab has been shown to be efficacious in the treatment of those with intestinal BD. Small (20 patients) non-randomized, open label prospective trials of adalimumab in the treatment of intestinal BD have demonstrated that 60% of patients have marked improvement in symptoms at 52 weeks with complete remission in 20% of patients at weeks 24 and 52. Additionally, adalimumab has been shown to be effective in treating extra-intestinal manifestations of BD.[6] Studies evaluating infliximab have demonstrated efficacy in the treatment of BD. It has been of particular benefit in the treatment of ocular manifestations in the setting of potentially sight threatening ocular involvement.[7] However, it has also been used in the treatment of intestinal manifestations efficaciously as well.[8]

Infliximab has been proved to be efficacious in the treatment of intestinal BD by multiple studies.[8,9] However, it is common for patients to be non-responders to initial treatment with Infliximab like the patient in our case. In a retrospective study by Kinoshita et al., patients starting Infliximab therapy with gastrointestinal bleeding, fevers, increased disease activity score for intestinal BD (DAIBD), and fulminant disease were significant, non-independent predictors of failure to respond to infliximab therapy at 10 weeks. Additionally, endoscopic evidence of disease activity at anastomoses was a significant predictor as well.[9] Other studies have demonstrated ileal involvement of disease as a potential predictor of Infliximab non-response.[8] Loss of response is a common adverse event in the treatment of inflammatory disorders with TNFα inhibitors, which can be overcome by adjustments of dosing. The mechanism of loss of response to TNFα inhibitors is thought to be secondary to the formation of antibodies to the medication, which leads to either blocking of the drug activity or faster drug clearance as evidenced by lower drug trough levels.[10] In patients treated with Infliximab for inflammatory bowel diseases, antibodies against the medication form in a significant proportion of patients with nearly 30% requiring adjustments to their treatment.[11] Current evidence suggests that there may be clinical benefit to monitoring of drug troughs and antibody levels during treatment with TNFα inhibitors.[10]

Whether infliximab at high-dose is more effective than adalimumab at regular dose, as suggested by our case, remains unclear. Increasing the dose of infliximab has previously shown to be efficacious in inducing remission of intestinal BD.[9] At this time, there have been no studies to compare the efficacy of infliximab versus adalimumab in the treatment of intestinal manifestations of BD. A multicenter retrospective study of 124 patients performed by the French Behçet Network demonstrated complete or partial remission in 83.3% of patients treated with infliximab that demonstrated intestinal manifestations of BD. Overall, treatment with a TNFα inhibitor led to complete or partial remission in 77.8% of patients treated with any TNFα inhibitor. However, none of the patients with intestinal manifestations were treated with adalimumab as initial therapy. Treatment with a TNFα inhibitor and an immunosuppressive agent showed improvement in intestinal manifestations of BD over treatment with TNFα inhibitor monotherapy. However, this difference was not statistically significant.[3] In all other manifestations of BD, infliximab and adalimumab were shown to be equally efficacious.[3]

CONFLICTS OF INTEREST DISCLOSURE

The authors have declared no conflicts of interest.

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