ACG CASE REPORTS JOURNAL

CASE REPORT | INFLAMMATORY BOWEL DISEASE

Tacrolimus Therapy for Ulcerative Colitis-Associated Post-Colectomy Enteritis

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Abstract

Ulcerative colitis (UC)-associated pan-enteritis is a newly identified clinical entity that occurs almost exclusively after colectomy. Characterized by diffuse small bowel mucosal inflammation not compatible with Crohn's disease, the optimal treatment modality for this condition is unknown. Tacrolimus is a potent calcineurin inhibitor that has been successfully used in the treatment of UC. We describe a case of severe refractory pan-enteritis after colectomy for UC that was successfully treated with oral tacrolimus after failing intravenous corticosteroid treatment. Tacrolimus may be a safe and effective treatment modality for diffuse enteritis after colectomy in UC patients.

Introduction

Ulcerative colitis (UC) has been traditionally characterized by mucosal colonic inflammation, with small bowel involvement limited to post-colectomy pouchitis or backwash ileitis. Recently, several authors have reported UC-related pan-enteritis, typically following colectomy for UC.[1–3] Capsule endoscopy and small bowel biopsy studies have demonstrated significantly increased small bowel inflammation, specifically in the subset of UC patients who had previously undergone colectomy.[4,5] As such, upper endoscopy would be warranted in the diagnostic evaluation of UC patients who present with abdominal symptoms after surgery.[6] Proposed treatment regimens for UC-related enteritis include mesalamine, azathioprine, cyclosporine, corticosteroids, and tumor necrosis factor alpha (TNFα) antagonists.[7,8] There is evidence that the calcineurin inhibitor tacrolimus can be a safe and effective long-term therapy for steroid-refractory inflammatory bowel disease (IBD).[9]

Case Report

A 43-year-old woman was diagnosed with pan-UC 6 years ago after 2 admissions for epigastric pain with elevated lipase but normal abdominal computed tomography (CT) scan, originally attributed to acute pancreatitis. To clarify the diagnosis, she underwent esophagogastroduodenoscopy (EGD) and colonoscopy with biopsies. Her EGD was endoscopically and histologically within normal limits. Her colonoscopy demonstrated mucosal friability, loss of vascular pattern, and diffuse, shallow ulceration throughout the colon consistent with pan-UC. Anti-tissue transglutaminase, anti-neutrophil cytoplasmic antibody, anti-saccharomyces cerevisiae antibody, *Cytomegalovirus*, and human immunodeficiency virus serologies were negative at the time of diagnosis. Stool cultures (including *Clostridium difficile*) and an ova and parasite examination were negative. She initially responded to prednisone and azathioprine induction; however, she did not sustain remission. Mesalazine, infliximab, and certolizumab were tried with minimal benefit. Ultimately, a total colectomy with end ileostomy was performed 3 years after diagnosis.

Approximately 3 months after her colectomy, she presented to our hospital with a 1-month history of worsening, daily, cramping, non-radiating, and intermittent epigastric pain. In the week prior to presentation, the pain

ACG Case Rep J 2014;2(1):33–35. doi:10.14309/crj.2014.76. Published online: October 10, 2014.

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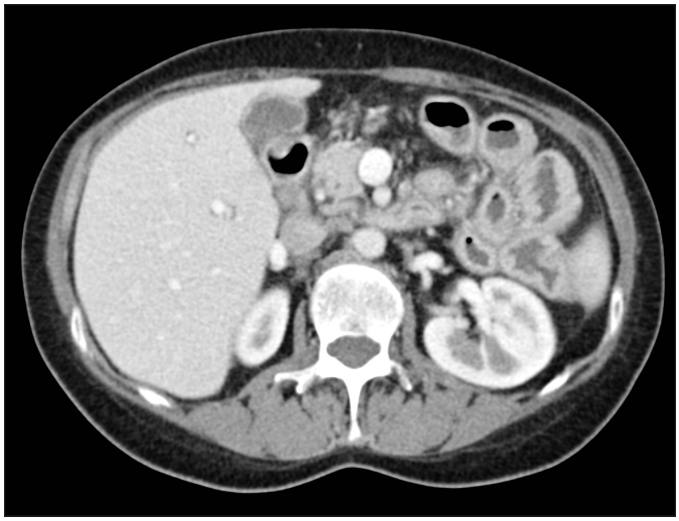

Figure 1. CT scan with contrast showing diffuse bowel wall edema and mesenteric lymphadenopathy. Bowel wall thickening extended throughout the small bowel.

was associated with nausea and vomiting of bile and undigested food. There were no aggravating or alleviating factors. Anorexia and difficulty maintaining adequate nutrition were evidenced by a 10-lb weight loss. Bloodwork revealed only a mild leukocytosis (11,400 x 103/μL) and an elevated lipase (758 U/L). An abdominal computed tomography (CT) with contrast, performed to investigate her abdominal pain, revealed diffuse small bowel thickening (Figure 1). Upper endoscopy and push enteroscopy to the proximal jejunum revealed a moderate gastritis and severe diffuse enteritis (Figure 2). The histopathology of the duodenal and jejunal biopsies revealed moderate to marked active chronic inflammation with cryptitis but no granulomas present, consistent with UC-associated pan-enteritis. The diffuse, continuous lesions were not characteristic of Crohn's disease.

The patient was treated with methylprednisolone 20 mg intravenously twice per day and parenteral nutrition; however, her symptoms persisted. Repeat enteroscopy and biopsies after 7 days again showed diffuse inflammation, severe in the duodenum and low-grade in the jejunum, with a normal ileum. Having shown neither symptomatic nor endoscopic improvement, she was started on tacrolimus (3 mg orally twice per day) for salvage therapy. Tacrolimus levels were titrated to between 4 and 8 ng/mL. Anti-TNF therapy was not initiated because the patient had previously failed 2 different anti-TNF agents. There was gradual clinical improvement such that the patient could be discharged home without the need for parenteral nutrition. A follow-up push enteroscopy showed further endoscopic and histologic improvement of the inflammation. After 6 months of monthly follow-up, she has remained clinically well on oral tacrolimus therapy.

Discussion

Diffuse enteritis after total proctocolectomy for UC has been recently described and is characterized by severe inflammation of the small bowel in patients who have undergone total proctocolectomy for ulcerative colitis.[1–3] Although many treatments have been proposed, the optimal treatment regimen for this condition remains undefined. A recent study by Hoentjen et al suggested a possible role for azathioprine in the long-term management after initial high-dose intravenous corticosteroids.[8]

Tacrolimus is a macrolide that inhibits calcineurin to suppress T-cells and the production of inflammatory cytokines. Systemic tacrolimus appears to be a safe and effective option for steroid refractory IBD.[9–11] The topical form has been used successfully for pyoderma gangrenosum and ulcerative proctitis.[12] The mechanism of tacrolimus is similar to that of cyclosporine A (CyA), which has also been used for refractory IBD. Both tacrolimus and CyA block the transcription of IL-2 by blocking the dephosphorylation of nuclear factor of activated T-cells.[11] When compared with CyA, tacrolimus has superior oral bioavailability and a more predictable dose response. Consequently, it has the advantage of easier initiation as an outpatient than CyA. It is generally well tolerated, with tremor being the most commonly reported side effect.[13] Other adverse effects, such as nephrotoxicity, are dose-dependent and typically resolve with cessation of therapy.[14] However, trials have been short in duration and small in number of patients, limiting conclusions regarding long-term safety in the treatment of IBD. Therefore, the de-

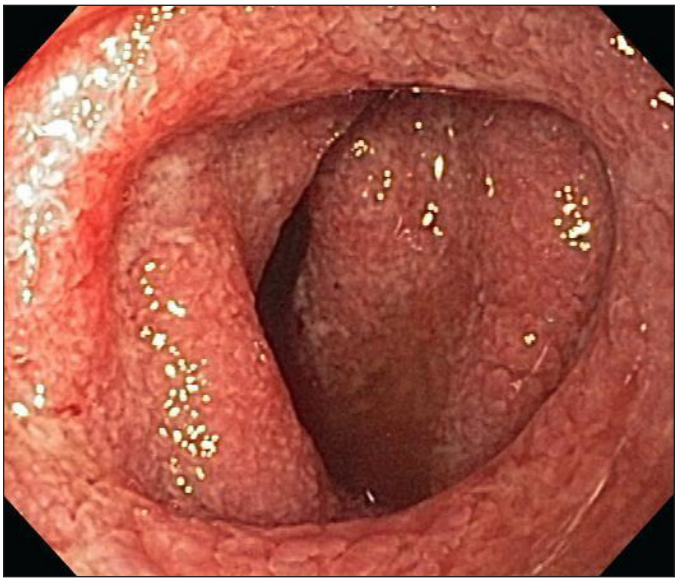

Figure 2. EGD at admission demonstrating severe diffuse enteritis in the duodenum.

cision to use tacrolimus must include careful consideration of the risks and benefits with close monitoring of patients for potential complications. Optimal tacrolimus dosing is not established for the treatment of this entity; therefore, we attempted to use the lowest possible doses to control symptoms, monitoring trough levels with a therapeutic target between 4 and 8 ng/mL. We suggest that further research is necessary to better understand the pathophysiology of enteritis associated with UC and the safety and efficacy of calcineurin inhibitors in the treatment of this condition.

Disclosures

Author contributions: B. Rush, L. Berger, and G. Rosenfeld wrote and edited the manuscript, and reviewed the literature. B. Bressler wrote, edited, guided the clinical relevance of the manuscript. B. Rush is the article guarantor.

Financial disclosure: None to report.

Informed consent was obtained for this case report.

Received: October 9, 2013; Accepted: July 30, 2014.

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