

Severe Enteropathy From Mycophenolate Mofetil

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Abstract

The adverse effects of mycophenolate mofetil on the colon are well known. However, isolated small intestinal involvement resulting in diarrhea and severe weight loss is infrequently reported in the literature. We present the case of a 45-year-old woman on mycophenolate mofetil following renal transplant, who presented with abdominal pain and weight loss. An esophagogastroduodenoscopy and colonoscopy with biopsies were normal. A small bowel capsule study revealed extensive enteropathy of jejunum and ileum that was confirmed on a push enteroscopy with biopsies. Her symptoms completely resolved after being switched to enteric-coated mycophenolic acid.

Introduction

Mycophenolate mofetil is frequently used in solid organ, bone marrow, and stem cell transplant recipients to decrease the risk of graft rejection. Gastrointestinal toxicity is the most common dose-limiting side effect of this medication.¹ Colonic involvement from mycophenolate mofetil is commonly reported in the literature; however, there is limited data on isolated involvement of the small intestine, and the pathological features of these lesions are poorly understood.

Case Report

A 45-year-old woman with history of gastroesophageal reflux disease, gastroparesis, irritable bowel syndrome, and iron-deficiency anemia presented with a chief complaint of mild, non-radiating, post-prandial epigastric pain that had significantly worsened over the last few months and was partially relieved by antacids. She underwent renal transplant 16 years ago after renal failure from glomerulonephritis. She reported mild, intermittent diarrhea since then, which had worsened over the last year with 5-6 large-volume, non-bloody bowel movements daily. In addition, she reported nausea, decreased appetite, fatigue, and a 9-kg unintentional weight loss in the last year. Her medications include mycophenolate mofetil 1 g twice daily (started post-transplant), tacrolimus 3 mg daily, prednisone 2.5 mg daily, acyclovir 400 mg twice daily, dexamethasone 60 mg daily, ranitidine 75 mg twice daily, and ferrous sulfate 325 mg daily. She denied NSAID use, smoking, alcohol abuse, illicit drug usage, or significant family history.

The patient's examination was unremarkable. Fecal leukocyte count, fecal trypsin, stool culture, stool *Clostridium difficile* toxin, and ova and parasites were negative. The laboratory tests revealed anemia with hemoglobin of 7.3 g/dL. Iron studies suggested anemia of chronic disease. Anti-tissue transglutaminase antibodies were negative. On esophagogastroduodenoscopy, gastric biopsies were normal. Mild scalloping was observed in the second part of the duodenum with biopsies negative for celiac disease. A colonoscopy was performed to the cecum, but the terminal ileum could not be intubated secondary to a redundant colon with looping. Colonic biopsies were negative

ACG Case Rep J 2016;3(2):101-103. doi:10.14309/crj.2016.13. Published online: January 20, 2016.

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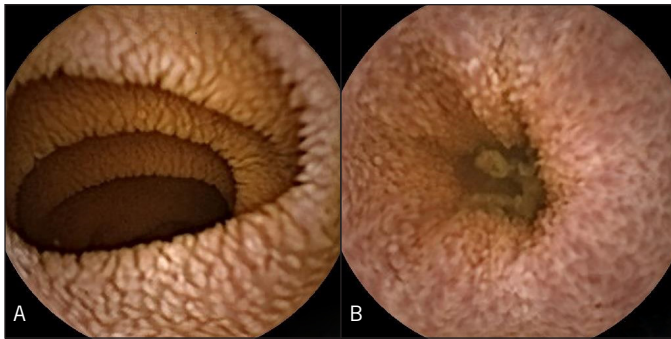


Figure 1. Small bowel capsule study showing the (A) proximal jejunum and (B) proximal ileum.

for any evidence of colitis or cytomegalovirus infection. The patient was advised to take loperamide daily, but she continued to experience worsening symptoms. Small bowel series was performed, showing non-specific irregularity of the terminal ileum suggestive of an inflammatory process. A capsule endoscopy showed scalloped mucosal folds in the duodenum and proximal jejunum, and moderate to severe mucosal congestion, granularity, and cobblestoning with luminal narrowing involving the distal jejunum to the distal ileum (Figure 1). Two days after capsule ingestion, she was admitted with a small bowel obstruction that was medically managed.

Repeat colonoscopy showed a constricted terminal ileum with patchy erythema and inflammation concerning for Crohn's disease; however, biopsies were normal. A small bowel push enteroscopy revealed duodenal and jejunal mucosal scalloping and congestion. Biopsies from the jejunum showed patchy villous blunting, lamina propria plasmacytosis, and apoptosis. One of the duodenal biopsies also revealed dilated crypts with necrotic debris in the lumen, which raised the possibility of small bowel injury from mycophenolate mofetil (Fig-

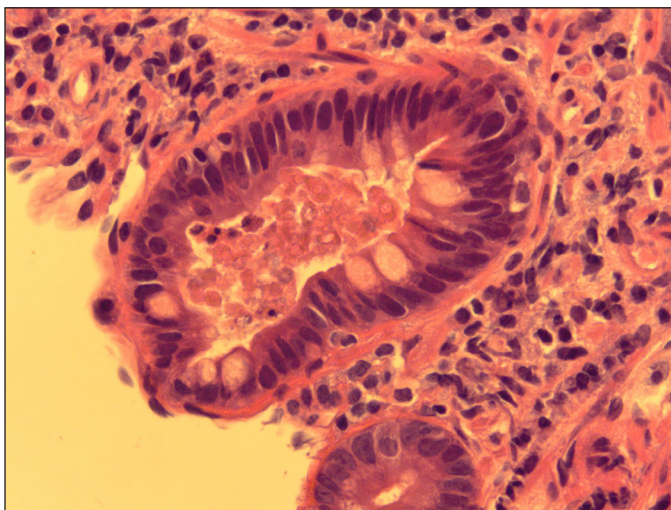


Figure 2. Biopsy of duodenum with H&E stain at x40 magnification demonstrating dilated duodenal crypt containing necrotic debris.

ure 2). There was no evidence of celiac disease or Whipple disease on the small bowel biopsies. Mycophenolate mofetil was discontinued, and the patient was switched to mycophenolate sodium. Her diet was gradually advanced and she was discharged home.

One month later, the patient reported significant improvement of her abdominal pain, diarrhea, and appetite, with subsequent weight gain. At the most recent follow up, she had regained nearly 9 kg, and had no gastrointestinal complaints; the hemoglobin returned to normal at 13 g/dL.

Discussion

Mycophenolic acid is a frequently used immunosuppressant in post-transplant patients and various autoimmune conditions. It acts by limiting the proliferation of B and T lymphocytes.² Therapeutic formulations of mycophenolic acid include mycophenolate mofetil and the enteric-coated mycophenolate sodium, also known as Myfortic (Novartis Pharmaceuticals, Basel, Switzerland).³ Mycophenolate mofetil is frequently associated with diarrhea, but can also cause abdominal pain, nausea, vomiting, dyspepsia, and anorexia.^{1,3} The reported incidence of gastrointestinal toxicity is 40-85%, and is the most common reason for drug discontinuation.² Discontinuation of mycophenolate mofetil can triple the risk of transplant rejection, while a dose reduction of $\geq 50\%$ doubles the risk of rejection.⁴ Thus, patients should be monitored for any adverse gastrointestinal symptoms.⁴

Side effects of mycophenolate mofetil have been attributed to its systemic toxicity. However, it is more likely to result from the mechanical injury of the gastrointestinal mucosa from N-(2-hydroxyethyl) morpholine, a metabolic product of mycophenolate mofetil, and acyl-MPAG, a toxic metabolite of mycophenolic acid.² Tacrolimus and acyclovir can potentially worsen toxicity by increasing the serum concentration of mycophenolate. On the contrary, proton pump inhibitors and antacids may decrease the serum concentration and the therapeutic efficacy of mycophenolate.

The adverse effects of mycophenolate mofetil on the colon are well-described in the literature, and can include graft-versus-host disease (GVHD), ischemic or nonspecific colitis, or a presentation mimicking inflammatory bowel disease.³ However, there have been few articles describing isolated involvement of the small intestine. Most of the literature points toward mycophenolate mofetil as the most common reason for duodenal villous atrophy in solid organ transplant patients presenting with chronic diarrhea.⁵ Small intestinal lesions include mucosal inflammation, erosions, and ulcerations.⁶ Small bowel injury can cause distortion, apoptosis, and crypt dilatation with neutrophils and eosinophils, and edematous lamina propria with scant inflammatory cells

on pathologic examination.⁷ These findings can resemble GVHD; pathological findings that can favor a diagnosis of mycophenolate mofetil toxicity over GVHD include high concentration of eosinophils in lamina propria with scarce apoptotic microabscesses and endocrine cell aggregates.⁸

Enteric-coated mycophenolate sodium, designed to delay the release of mycophenolic acid, is as effective as mycophenolate mofetil in preventing graft rejection with a comparable safety profile.⁹ A study of 397 organ graft recipients demonstrated that gastrointestinal symptoms from mycophenolic acid toxicity may improve after conversion to enteric-coated mycophenolate sodium, although other data suggests that there is no improvement.¹⁰⁻¹² Our case suggests that patients with biopsy-proven small intestinal toxicity from mycophenolate mofetil may have marked improvement of symptoms after being switched to enteric-coated mycophenolate sodium. In patients with clinical improvement, repeat capsule endoscopy is not necessary as the lesions may take almost 2 years to heal.⁶

Disclosures

Author contributions: All authors contributed to the literature search and approved the final version of the manuscript. A. Jehangir wrote the initial manuscript and is the article guarantor. B. Shakh revised the manuscript. J. Hunt provided the pathology slides, labeled the captions, and reviewed the manuscript. A. Spiegel edited the manuscript, and provided images of the small bowel capsule study.

Financial disclosure: None to report.

Informed consent was obtained for this case report.

Received May 11, 2015; Accepted October 6, 2015

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