Mycophenolate-Associated Sprue-Like Intestinal Disease Evolving into Collagenous Sprue

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Abstract A 43-yr old female with two prior renal transplants for renal failure associated with diabetes, retinopathy and coronary artery disease developed diarrhea. Her medications included mycophenolate mofetil, an immunosuppressive medication documented to cause sprue-like mucosal changes in the small intestine. Later studies revealed a small intestinal mucosal lesion characterized by marked crypt hyperplasia, villous atrophy and increased intra-epithelial lymphocytes. Serological studies for celiac disease were negative and repeated biopsies despite a strict gluten-free diet, revealed histopathological persistence of a severely abnormal sprue-like enteropathy. Eventually, further biopsies of her small intestine revealed superimposed changes characterized by dense sub-epithelial collagen deposits histochemically staining positive for trichrome, typical of collagenous sprue and representing an expansion of published pathological features of mycophenolate-associated small intestinal mucosal disease.

Keywords: celiac disease, sprue-like intestinal disease, collagenous sprue, mycophenolate, immunosuppressants, refractory sprue

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1. Introduction

Sprue-like intestinal disease has been reported in a wide array of clinical settings, including solid organ transplant recipients [1]. About 2 decades ago, diarrhea and weight loss were first associated with small intestinal villous atrophy (resembling untreated celiac disease) in a renal transplant recipient during treatment with mycophenolate mofetil [2]. A number of other drugs have caused similar small intestinal changes [3]. In most, celiac serological testing have been negative and, usually, a gluten-free diet does not resolve symptoms or improve the abnormal biopsy changes. Following a prior rejection episode that resulted in a second renal transplant in the patient described here, an insidious and initially intermittent diarrheal disorder developed during mycophenolate treatment that eventually became continuously present. Small intestinal biopsies showed features of untreated celiac disease, however, serological studies for celiac disease were negative. After a prolonged gluten-free diet, repeated biopsy studies on mycophenolate treatment failed to show improvement, and later, typical histopathological features of collagenous sprue.

2. Case Report

A 43 year-old female was referred for severe and worsening diarrhea over 3 years associated with an estimated weight loss of 20 kg. Initially, her diarrhea was intermittent, but then became continuous.

Past history included type 1 insulin-dependent diabetes (diagnosed at age 11) complicated by retinopathy and nephropathy. She had a right renal transplant in 1994, then after rejection, a left renal transplant in 1996. Subsequently, she received immunosuppression with tacrolimus 1 mg every 12 hours, mycophenolate mofetil 1 g twice daily and prednisone. She also had coronary artery disease treated with bypass grafts and 2 cerebrovascular accidents. There was no recent history of antimicrobial use or foreign travel.

Figure 1. Small intestinal biopsy showing typical features of untreated celiac disease with crypt hyperplastic villous atrophy, including increased numbers of intra-epithelial lymphocytes. Despite treatment with a gluten-free diet, no improvement in the histopathological features was observed. Hematoxylin and eosin, magnification X 5

Multiple biopsies from the proximal small bowel showed features of untreated celiac disease including severely flattened villi, increased cellularity of the lamina propria, crypt hyperplasia and increased intra-epithelial...
lymphocytes (i.e., Marsh 3) (Figure 1). Fecal studies for microbial and parasitic agents were negative. Routine blood studies, including immunoglobulins, and measurement of vasoactive intestinal polypeptide were normal. A CT scan of the abdomen was normal with no lymphadenopathy and an abdominal MRI with gadolinium was normal. Although celiac serological studies were all negative (anti-gliadin, anti-endomysial, anti-tissue transglutaminase), diarrhea appeared to diminish on the gluten-free diet. Colonoscopy was normal, including colonic biopsies, but an ileal biopsy revealed that intraepithelial lymphocytes were slightly increased [4].

Within a month of these studies, however, recurrent and sometimes severe diarrhea developed, thought initially to be related to “accidental” ingestion of wheat from contamination of her bread-making equipment. After 8 months of continued symptoms despite a gluten-free diet, multiple repeated proximal small intestinal biopsies showed no improvement. Hospitalization later resulted due to worsening diarrhea and multiple trials in-hospital on a gluten-free diet failed including added lomotil, codiene, budesonide and octreotide. However, an increased prednisone dose to 30 mg daily provided temporary relief and permitted discharge and passage of a single solid stool. Unfortunately, as prednisone was tapered to 15 mg daily, diarrhea became severe again with development of marked fluid depletion and weight loss of 5 kg within 24 hr. Weakness and fatigue with rapid heart palpitations were noted but no fever. She was re-hospitalized for urgent fluid replenishment and correction of marked hypokalemia. After correction, repeat endoscopy and multiple biopsies from several proximal small intestinal sites showed features of collagenous sprue (Figure 2). Eventually, she was discharged on added dose of prednisone. Unfortunately, renal failure, attributed to diabetes, progressed and further transplantation was considered, but the patient opted for palliative care and no further investigations were done. She eventually developed profound sepsis and died in December 2006.

![Figure 2. Later small intestinal biopsy showing changes of collagenous sprue. A histochemical stain with Trichrome was positive, while other histochemical stains, including Congo Red for amyloid, were negative. Trichrome, magnification X 10.](image)

### 3. Discussion

Mycophenolate mofetil, given as part of a maintenance immunosuppression regimen to solid organ transplant recipients, may cause diarrhea, weight loss and other features of intestinal toxicity. In some reports, up to 40% of renal transplant recipients on this medication have been affected [5,6,7]. Initially, colonic mucosal injury was noted [7]. This colitis is mimicked by other forms of colitis, including graft-versus-host disease with crypt distortion and, in some, impressive crypt cell apoptosis. In those without colonic mucosal inflammatory change, further studies for diarrhea often led to the discovery of small intestinal mucosal disease [7]. These small intestinal changes caused significant pathological features, often features of graft-versus-host disease [9,10], occasionally an erosive enteritis with colitis [11], and sometimes, as shown in the present patient, changes were documented mimicking the pathological features typical of untreated celiac disease. In 1998, Ducloux and his colleagues provided the first description of villous blunting of the duodenal mucosa with crypt hyperplasia in a renal transplant recipient on mycophenolate [2]. Similar features were later reported by Weclawia et al [12] in a case series of patients with solid organ transplants and by Kamar et al in 4 cases with severe diarrhea and villous atrophy induced by mycophenolate [13]. Similar sprue-like changes were reported earlier by Zeigler et al [14] using another immunosuppressive drug, azathioprine, and by others in orthotopic liver transplant recipients on mycophenolate therapy [15]. These findings of a sprue-like intestinal disorder histologically mimicking untreated celiac disease, were often accompanied by negative celiac serological studies and a failed response to a gluten-free diet. These findings have also been reported in patients with withdrawal of the medication, similar to olmesartan-associated enteropathy [16]. A previous report emphasized the high frequency of medication-associated sprue-like enteropathy, about 26%, in patients presenting with diarrhea, weight loss and biopsy changes of untreated celiac disease [7], so immunosuppressive regimens in patients with diarrhea (indeed, all medications) should always be carefully scrutinized before attributing the pathological changes to celiac disease or, later, particularly after treatment with a gluten-free diet, to a treatment-resistant or refractory celiac disease.

To date, a long latency period from onset of mycophenolate use to clinical and pathological changes has been described. Others have recently noted that clinical features may eventually be reversible in some patients with withdrawal of the medication, similar to olmesartan-associated enteropathy [15]. The patient here, however, was found to have a further histopathological change with the appearance of collagenous sprue, similar to the sequence of changes initially described in collagenous sprue apparently unrelated to medication [16]. Moreover, the association with drug-induced collagenous sprue is similar to recently detected olmesartan-induced collagenous sprue [17].

In conclusion, this report documents a further case of severe sprue-like enteropathy associated with mycophenolate immune suppression in a renal transplant recipient but expands the histopathological spectrum to include the small bowel histopathological features of collagenous sprue.
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