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Celiac-like Enteropathy Associated With Mycophenolate Sodium in Renal Transplant Recipients

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Background. Although colonic injury is a well-known complication of mycophenolic acid (MPA), the involvement of the upper gastrointestinal tract is less extensively documented. We present the occurrence of celiac-like duodenopathy manifested as a severe diarrhea syndrome in 2 renal transplant recipients on enteric-coated mycophenolate sodium. **Methods.** The patients belong to a setting of 16 renal transplant recipients under MPA suffering from chronic diarrhea in the absence of MPA-related colitis. **Results.** Both patients had a history of persistent diarrhea with significant weight loss. Colonic mucosa was unremarkable, whereas duodenal biopsies revealed celiac-like changes with increased epithelial cell apoptosis. Clinical symptoms completely resolved, and follow-up biopsies demonstrated normalization of histology after enteric-coated mycophenolate sodium withdrawal and switching to azathioprine. **Conclusions.** Celiac-like enteropathy seems to represent a rare side effect of MPA-associated immunosuppressive therapy and should be taken into account in the differential diagnosis of diarrhea in transplant recipients treated with MPA particularly in the absence of MPA-related colitis. As macroscopic lesions are usually missing, blind duodenal biopsies are necessary to establish the diagnosis.

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Mycophenolic acid (MPA) in its 2 available formulations, mycophenolate mofetil (MMF) and enteric-coated mycophenolate sodium (EC-MPS), is commonly used in solid organ transplantation as part of the maintenance immunosuppressive regimen. Gastrointestinal (GI) toxicity is the most common side effect occurring in up to 45% of renal transplant recipients.[1,2] The pattern of colonic injury has been well described as MMF-associated colitis characterized by crypt distortion and prominent crypt cell apoptosis mimicking inflammatory bowel disease and, less often, graft-versus-host disease (GVHD).[2,3] The upper GI tract is less frequently involved, whereas only few reports refer to isolated involvement of the small intestine causing chronic diarrhea and severe weight loss with no sufficient information available regarding pattern of injury.[4] In the present short communication, we report the development of celiac-like enteropathy in 2 renal transplant patients under EC-MPS treatment with a clinical history of chronic diarrhea and substantial weight loss.

MATERIALS AND METHODS

The cases to be presented belong to a series of 70 renal transplant recipients under MMF or EC-MPS and persistent diarrhea who underwent colonoscopy between 2003 and 2016 at Laiko General Hospital (Athens, Greece). Patients with infectious colitis have been excluded, whereas no patient had a clinical history of inflammatory bowel disease. In 54 (77.15%) patients, MPA-related colitis was diagnosed histologically, whereas in 16 (22.85%) patients colonic biopsies

did not display any significant changes. These 16 patients underwent upper GI endoscopy, and duodenal biopsies were obtained from different parts of the duodenum, including bulbus. Histological evaluation showed no significant findings in 3 cases, nonspecific duodenitis in 9 cases (1 with mild villous atrophy), peptic duodenitis in 2, and in the remaining 2 cases, celiac-like changes were identified. Immunohistochemical staining was performed for intraepithelial T lymphocytes assessment using anti-CD3 and anti-CD8 antibodies (DAKO A/S, Denmark). The number of CD3+ intraepithelial lymphocytes (IEL)/100 villous epithelial cells (IEL count) was evaluated. Epithelial cell apoptosis was separately estimated in a total of 100 villi and 100 crypts on hematoxylin and eosin (H&E). Apoptotic index was defined as the mean number of apoptotic bodies per villous and crypt.

The study was performed in accordance with the Declaration of Helsinki and with the approval of the local ethics committee. Informed consent was obtained from both renal transplant patients whose cases were presented in this manuscript.

RESULTS

Case 1

A 76-year-old man presented 16 months after kidney transplantation from deceased donor with intermittent watery, nonbloody diarrhea, and substantial weight loss. Before transplantation, he was 8 years on hemodialysis due to end-stage renal disease attributed to presumed glomerulonephritis. His daily maintenance immunosuppressive regimen comprised 1080-mg EC-MPS, 4-mg tacrolimus, and 4-mg methylprednisolone. He denied use of nonsteroidal anti-inflammatory drugs and antibiotics, alcohol abuse, recent travel, or similar symptoms among family members.

Symptoms manifested 13 months posttransplantation with sudden onset of semiwatery stools, approximately 5 per day. At presentation, almost 3 months after diarrhea onset, the patient complained of severe and almost daily episodes of watery diarrhea associated with abdominal cramps and low-grade fever as well as of weigh loss of approximately 10 kilos. Blind colonic biopsies did not display any significant changes. Considering that the absence of histological evidence does not rule out the possibility of MPA-induced colitis, the dose of EC-MPS was reduced to 720 mg daily, whereas the rest of the immunosuppressive regimen remained unchanged. After 3 months of clinical improvement, intermittent episodes of large-volume watery diarrhea reappeared. In addition, the patient reported nausea, decreased appetite, fatigue, and further weight loss of at least 10 kilos after his last visit. Of note, he was already following a gluten-free diet for at least 4 months with no beneficial effect. On admission, he had a body mass index of 19 kg/m^2 with significant muscle wasting and blood pressure of 100/70 mm Hg. Laboratory investigation showed normocytic, normochromic anemia with hemoglobin of 9.6 g/dL, leukocyte count of 4.9×10^5/L, serum creatinine level of 4.17 mg/dL (367 μmol/L), and serum albumin 2.7 g/dL (27 g/L). Fecal leukocyte count, stool cultures, stool *Clostridium difficile* toxin, and examination for parasites were repeatedly negative. Cytomegalovirus was excluded by quantitative polymerase chain reaction in plasma and immunohistochemically in all biopsy specimens.

Esophagogastroduodenoscopy and colonoscopy did not show any macroscopic abnormalities. However, blind duodenal biopsies revealed mild villous atrophy and increased number of intraepithelial T lymphocytes expressing CD3 and CD8 immunohistochemically (Figures 1A and B). These findings were compatible with celiac-like duodenopathy analogous to type 3A of the modified Marsh classification.[5] In addition, apoptotic index was found increased, especially in the epithelium of the villi (Figure 1C). Histological findings are shown in detail in Table 1. Colonic biopsies from different parts of the colon exhibited mild nonspecific changes.

Small bowel capsule examination was normal. Celiac serologies (IgA and IgG gliadin antibodies, endomysium antibody, tissue transglutaminase antibody) were negative while

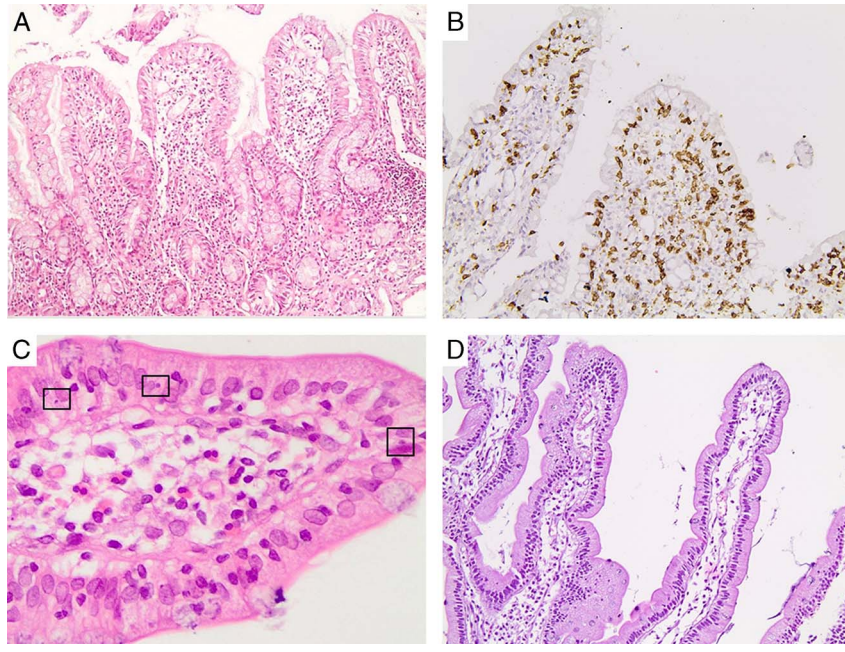

FIGURE 1. Case 1. A, Duodenal mucosa with mild villous atrophy (H&E ×100). B, Intraepithelial lymphocytosis (CD3 immunostain ×200). C, Apoptotic bodies outlined in squares (H&E ×400). D, Normal duodenal mucosa (H&E ×100).

TABLE 1.

Histological findings

	Villous atrophy	IEL count mean (range)	Villi apoptotic count/index	Crypts apoptotic count/index	Eosinophils LP count	Neutrophils LP count	Lymphoplasmacytic infiltrate
Case 1	Mild	53.73 (32-93)	327/3.27	29/0.29	≤10/hpf	≤2/hpf	Moderate
Case 2	Moderate	60.4 (36-90)	560/5.6	55/0.55	≤10/hpf	≤5/hpf	Mild

IEL count: number of intraepithelial CD3+ lymphocytes/100 villous epithelial cells.

Villi apoptotic count: number of apoptotic bodies/100 villi.

Villi apoptotic index: mean number of apoptotic bodies/villous.

Crypts apoptotic count: apoptotic bodies/100 crypts.

Crypts apoptotic index: mean number of apoptotic bodies/crypt.

LP, lamina propria; hpf, high power field.

consuming gluten. HLA genotyping was inconsistent with celiac disease.

Enteric-coated mycophenolate sodium was discontinued, and the patient was switched to azathioprine 2 mg/kg once daily. After cessation, GI symptoms resolved completely within 1 week. The patient also underwent gluten challenge without symptom recurrence. Follow-up laboratory tests showed recovery of renal function and correction of anemia. One month later, the patient reported significant improvement of his appetite with subsequent weight gain. A follow-up biopsy, 9 months after EC-MPS withdrawal while consuming gluten-containing diet, revealed normalization of villous atrophy and of IEL count with no evidence of abnormal apoptotic rate (Figure 1D). At his last visit, 20 months after EC-MPS withdrawal, the patient had regained nearly 20 kilos and had no GI complaints.

Case 2

A 70-year-old male patient, who had received a renal graft from a deceased donor, developed a posttransplant progressively aggravating diarrhea syndrome. Before transplantation, the patient was on hemodialysis for 4 years due to end-stage renal disease on a background of unknown nephropathy. Patient's daily maintenance immunosuppressive regimen comprised 1080-mg EC-MPS, 1-mg tacrolimus, and 5-mg prednisolone. There was no history of nonsteroidal anti-inflammatory drugs and antibiotics use, alcohol abuse, recent travel, or similar symptoms in his household.

Patient's symptoms began 6 months after kidney transplantation when he reported loose stools and rare episodes of nonbloody watery diarrhea with no other GI or systemic complaints. The dose of EC-MPS was reduced to 720 mg daily. Afterward, GI symptoms resolved completely for 2 and half years. Subsequently, diarrhea recurred and manifested with up to 6 episodes of severe watery, nonbloody stools per day. The patient also complained of abdominal colicky pain, anorexia, bloating, and intermittent nausea and stated weight loss of approximately 5 kilos. Physical examination revealed a body mass index of 24 kg/m^2. Laboratory investigation showed hemoglobin of 13 g/dL, leukocyte count and CRP within the normal range, a serum creatinine level of 2.3 mg/dL (202 μmol/L), and serum albumin of 3.5 g/dL (35 g/L). Fecal leukocyte count, stool cultures, stool *Clostridium difficile* toxin, and examination for parasites were repeatedly negative. Cytomegalovirus was excluded by quantitative polymerase chain reaction in plasma and immunohistochemically in all biopsy specimens.

Colonic biopsies exhibited mild nonspecific colitis, whereas esophagogastroduodenoscopy was unremarkable. However, blind duodenal biopsies revealed moderate villous atrophy and increased number of intraepithelial CD3, CD8-positive T lymphocytes (Figures 2A, B). These findings were compatible with celiac-like duodenopathy corresponding to type 3B according to the modified Marsh classification.[5] A high apoptotic index predominantly in the villous epithelium constituted an additional finding (Figure 2C). All histological findings are included in Table 1.

Small bowel capsule did not reveal any changes. Celiac serology and HLA genotyping for DQ2/DQ8 were negative. Nevertheless, gluten-free diet was instituted for at least 3 months with no significant clinical response. Subsequently, EC-MPS was discontinued, and the patient was switched to azathioprine 2 mg/kg once daily. After the switch, GI symptoms resolved completely within 1 week and did not recur after gluten challenge. Follow-up laboratory studies showed return of renal function to baseline values. One month later, the patient reported significant improvement of his appetite with subsequent weight gain of approximately 6 kilos. Repeat endoscopy was performed 8 months after EC-MPS withdrawal while consuming gluten-containing diet and demonstrated restitution of all pathological lesions (Figure 2D). At the most recent follow-up, 20 months later, he was in excellent clinical condition with no GI manifestations.

DISCUSSION

These 2 cases provide sufficient evidence of celiac-like duodenopathy as a highly potential, although rare, complication of EC-MPS in kidney transplant recipients. The clinical manifestations in both cases included severe chronic diarrhea and substantial weight loss. Serology and HLA genotyping for celiac disease were negative. Gastrointestinal endoscopy was unremarkable, and only blind duodenal biopsies made the final diagnosis. Histology exhibited a combination pattern of villous atrophy and intraepithelial lymphocytosis differing from genuine celiac disease by the coexistence of epithelial cell apoptosis and absence of prominent lymphoplasmacytic mucosa infiltrates.[5] Lack of crypt damage and the presence of increased number of IEL constituted differential diagnostic criteria from GVHD.[6] Besides apoptosis, there were no other similarities with the histological features encountered in our cohort of MMF-associated colitis.[3] Complete clinical response and normalization of histology were achieved after EC-MPS withdrawal.

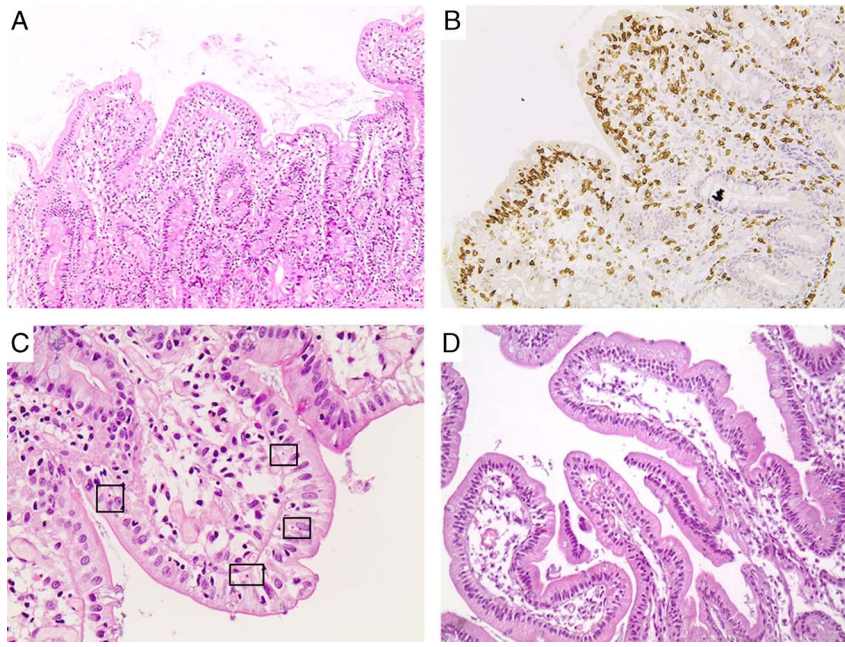

FIGURE 2. Case 2. A, Duodenal mucosa with moderate villous atrophy (H&E ×100). B, Intraepithelial lymphocytosis (CD3 immunostain ×200). C, Apoptotic bodies outlined in squares (H&E ×400). D, Normal duodenal mucosa (H&E ×100).

Mycophenolic acid has the potential to affect both the upper and lower GI tracts, although large bowel involvement clearly predominates presenting a rather common side effect in renal transplant patients.[1-4] Mycophenolic acid–associated colitis is widely recognized as a distinct drug-induced colitis, whereas the spectrum of endoscopic and histological features has been well documented.[2,3,7] Limited data are available regarding upper GI tract involvement, including duodenum, in symptomatic solid organ mainly kidney transplant patients on MPA. The first histological description of MPA-associated damage of the duodenal mucosa was reported by Ducloux et al[8] in 1998 who described villous blunting and crypt hyperplasia in the duodenum of a kidney transplant patient receiving MMF. Subsequently, a similar observation derived from a large series of patients with chronic diarrhea and significant weight loss.[9] Duodenal villous atrophy was encountered in 16% of patients and was attributed to MMF and EC-MPS therapy in 86% of these cases. Mycophenolic acid withdrawal or dose reduction resulted in diarrhea cessation and normal histology in all patients but one. It should be mentioned that in a small number of cases, azathioprine has been implicated for chronic diarrhea and duodenal villous atrophy which resolved after drug discontinuation.[9,10]

Another specific finding identified as MPA-associated lesion not only in the lower but also in the upper GI tract is prominent apoptosis.[3,4,11] In a small series of 12 duodenal biopsies, 4 cases presented GVHD-like features associated with villous blunting.[11] In another study of 17 duodenal biopsies, 82% exhibited increased apoptotic counts (>2 apoptotic bodies/100 crypts) with or without mucosa abnormalities.[4] In 2 cases, mucosa changes were determined as celiac-like due to additional intraepithelial lymphocytosis.[4]

Our presented cases as well as the 2 aforementioned are the only reported cases diagnosed as celiac-like duodenopathy in the setting of symptomatic renal transplant patients receiving EC-MPS and MMF.[4] It should be stressed that the referred study was designed to evaluate mucosa injury and apoptotic counts in upper GI compared with normal controls. The fact that clinicopathological data both at baseline and during follow-up are largely missing renders our cases of prime importance in the presentation of an emerging drug-related entity.

Celiac-like duodenal pathology potentially associated with MPA therapy has been described in orthotopic liver transplant patients as well.[12] Four of 16 patients showing abnormal histology were on MPA and displayed celiac-like changes combining villous atrophy and intraepithelial lymphocytosis in addition to increased apoptotic and endocrine cell counts and lamina propria eosinophils. Similar to our presented cases, MPA discontinuation or dose reduction resulted in improvement of symptoms within 1 to 3 weeks. However, follow-up biopsies were not available.[12]

Celiac-like enteropathy represents an increasingly recognized broad clinical and pathological spectrum of possibly unrelated disorders that share celiac-like changes in small intestinal biopsies and respond to withdrawal of the offending agent with clinical and histopathological improvement and not to a gluten-free diet.[13,14] Among the most frequently recognized celiac-like enteropathies are "medication-related." The list of implicated drugs is expanding and includes angiotensin receptor blockers, antimicrobials, chemotherapeutic, and immunosuppressive agents.[14] In a study evaluating adult patients with villous atrophy and negative celiac serology over a 10-year period, the 2 most common diagnoses were seronegative celiac disease (28%) and medication-related villous blunting (26%), the latter attributed to olmesartan in 16 of 19 cases, and MMF and methotrexate in the remaining 3 cases.[15]

Celiac-like duodenopathy seems to present a rare complication of immunosuppressive therapy with MPA manifesting few months to several years after medication initiation with persistent diarrhea and weight loss. A celiac-like histological pattern combined with apoptosis is encountered reminiscent of autoimmune enteropathy. One should be aware that this condition may be underdiagnosed because duodenal mucosa

may appear endoscopically normal. In addition, a precedent diagnosis of MMF-induced colitis usually renders upper GI endoscopy superfluous.

Our cases were both treated with EC-MPS, whereas most cases of villous atrophy including those with celiac-like enteropathy described so far in the literature received MMF.[4,9] Although the beneficial effect of switching from MMF to EC-MPS presents a common observation in graft recipients, there are findings demonstrating no significant clinical differences between these 2 MPA formulations.[16-18]

Complete resolution of histological lesions in our 2 cases few months after MPA withdrawal is in agreement with the experience on olmesartan-associated enteropathy.[19] The common course provides evidence of underlying drug-induced mechanisms different from those of celiac disease per se, which resides months and even years after initiation of a gluten-free diet.[14,20] Although the association between MPA and celiac enteropathy has not yet been clarified, robust literature data support a causative link.[9,21] The multiple properties of MPA imply a complex pathogenetic process and incriminate possible immunologic, toxic, and inflammatory mechanisms. The direct action of MPA is determined by its antiproliferative impact, whereas its metabolites display proinflammatory effects.[1] Acyl-MPA glucuronide, a toxic metabolite produced by GI cells, may be pathogenetically involved, although local metabolite concentrations have not been reported.[22] Mycophenolic acid–induced alteration in cytokine production, which potentially affects gut homeostasis, may also play a contributory role.[17,23] However, the long latency period between drug initiation and development of symptoms and in particular the presence of histological features indicative of T lymphocytes induced epithelial cell apoptosis support, an immune-mediated process. An underlying MPA-related immune dysregulation in association with an immune response to putative autoantigens, such as adducts formed by Acyl-MPA glucuronide metabolites or altered cellular proteins should be considered.[24] The latter hypothesis is strengthened by the recognition of immunological disorders of the small intestine, such as autoimmune enteropathy and common variable immunodeficiency, which share a common histological pattern on the background of immunodeficiency.[3,25]

In summary, celiac-like enteropathy seems to represent a rare side effect of MPA-associated immunosuppressive therapy and should be taken into account in the differential diagnosis of diarrhea in transplant recipients treated with MPA in particular in the absence of MPA-related colitis. As macroscopic lesions are usually missing, blind duodenal biopsies are necessary to establish the diagnosis. Clinical response appears to occur immediately after MPA withdrawal with complete reversal of mucosa lesions.

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