Mycophenolate mofetil-induced oral ulcerations in solid organ transplant recipients: A report of 3 cases

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Mycophenolate mofetil (MMF) is a potent immunosuppressive agent frequently used to prevent acute graft rejection in solid organ transplant recipients.[1-3] Common adverse effects of MMF include gastrointestinal disturbances, leukopenia, and an increased susceptibility to viral infections.[4] Rarely, oral ulcerations may occur in patients—especially solid organ transplant recipients—undergoing treatment with MMF.[5-11] We present 3 cases of MMF-induced oral ulcers in recipients of kidney, liver, and lung transplants.

Abbreviations used:

CMV:	cytomegalovirus
H&E:	hematoxylin-eosin
HSV:	herpes simplex virus
MMF:	mycophenolate mofetil
RPR:	rapid plasma reagin

CASE 1

A 68-year-old man with a history of polycystic kidney disease underwent bilateral cadaveric renal transplantation and was started on an immunosuppressive regimen consisting of MMF (2 g/d) and tacrolimus (16 mg/d). Eight months later, the patient was admitted to the hospital with acute renal failure and was noted to have multiple oral ulcers of unknown duration associated with severe oral pain and odynophagia. He denied a history of similar lesions, recent fevers, or myalgias.

On examination, 3 major aphthous ulcers (11 mm each) with surrounding erythema and petechiae were present on his soft palate. Laboratory values were significant for a white blood cell count of 3,700/mm^3, hemoglobin level of 9.4 g/dL, platelet count of 133,000/mm^3, and creatinine level of 2.0 mg/dL. Cultures of the oral lesions were negative for herpes simplex virus (HSV) types 1 and 2, cytomegalovirus (CMV), and fungus. Rapid plasma reagin (RPR) and HIV antibody testing results were nonreactive. Oral biopsy found nonspecific inflammatory changes on hematoxylin-eosin (H&E) staining. Direct and indirect immunofluorescence study findings were normal.

MMF was subsequently discontinued. After 4 days, the patient's oral ulcers decreased considerably in size, and he reported a significant reduction in his oral pain with an improved ability to eat and drink. After 9 days, complete healing of the patient's ulcers was observed. The patient has since remained off MMF with no recurrences of his ulcerations.

CASE 2

A 59-year-old woman with a history of cirrhosis secondary to α_1-antitrypsin deficiency received an orthotopic liver transplantation and was started on an immunosuppressive regimen consisting of MMF (2 g/d), tacrolimus (6 mg/d), and prednisone (2.5 mg/d). Five months later, the patient was admitted to the hospital for evaluation of multiple painful oral ulcerations and odynophagia of 6 weeks' duration. She denied a history of similar lesions, recent fevers, or myalgias.

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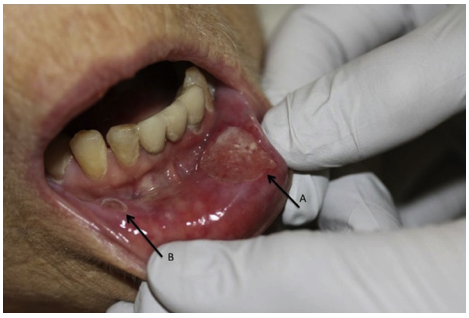

Fig 1. Multiple aphthous ulcerations on the inside of the lower lip (case 3). **A**, A 12-mm major aphthous ulceration. **B**, A 5-mm minor aphthous ulceration.

On examination, 2 major aphthous ulcers (12 mm each) with surrounding erythema were present on the inside of her lower lip, and one minor aphthous ulcer (5 mm) was noted on her right buccal mucosa. Laboratory values were significant for normal liver function tests with a white blood cell count of 4,300/mm^3, hemoglobin level of 9.2 g/dL, and platelet count of 112,000/mm^3. Cultures of the oral lesions were negative for HSV, CMV, and fungus. RPR and HIV antibody testing results were nonreactive. Oral biopsy found nonspecific inflammatory changes on H&E staining. Direct and indirect immunofluorescence findings were normal.

MMF was subsequently discontinued. After 4 days, the size of the patient's ulcers diminished considerably with significant improvement in her oral pain, and by 6 weeks, the ulcers had healed completely. The patient has since remained off MMF with no recurrences of her ulcerations.

CASE 3

A 65-year-old woman with a history of idiopathic pulmonary fibrosis underwent single lung transplantation. Postoperatively, she was started on an immunosuppressive regimen of MMF (1 g/d), cyclosporine (200 mg/d), and prednisone (40 mg/d). Ten months later, the patient was hospitalized after 2 weeks of weakness and decreased oral intake in the setting of multiple new ulcerations of her oral mucosa.

The patient denied a history of oral ulcers, recent fevers, or myalgias. She reported significant pain in her mouth and had lost 5 pounds over the previous 2 weeks because of an inability to swallow or eat food. She was initially prescribed oral fluconazole and viscous lidocaine, but these treatments failed to relieve her symptoms.

On examination, 2 minor aphthous ulcers (6 mm and 8 mm) were present on her right buccal mucosa, 1 minor aphthous ulcer (3 mm) was observed underneath her tongue, and 2 aphthous ulcers, 1 major (12 mm) and 1 minor (5 mm), were noted on the inside of her lower lip (Fig 1). Laboratory values were significant for a white blood cell count of 3.7 cells/mm^3, hemoglobin level of 7.0 g/dL, and platelet count of 11,000 cells/mm^3. Cultures of the oral lesions were negative for HSV, CMV, and fungus. RPR and HIV antibody results were nonreactive. Oral biopsy found nonspecific inflammatory changes on H&E staining. Direct and indirect immunofluorescence findings were normal.

MMF was subsequently discontinued. After 7 days, the patient's ulcers diminished considerably in size, and she reported a substantial decrease in her oral pain. Long-term follow-up could not be obtained, however, because the patient became critically ill during her hospitalization and died from hospital-acquired pneumonia.

DISCUSSION

The differential diagnosis of oral mucosal ulcerations in the immunocompromised patient includes infections (most commonly HSV), hematologic disorders, autoimmune and bullous diseases, and malignancies.[12] In our 3 patients, the workup for all such causes was uniformly negative, making MMF-induced aphthae a more likely explanation. In contrast to certain immunosuppressive agents, particularly mTOR inhibitors such as sirolimus—which are well known to cause oral ulcers[13]—MMF has only rarely been associated with such ulcers. To date, 7 case reports have been published describing this association, 6 of which involve solid organ transplant recipients.[5-11] In all cases, the development of oral ulcers was not associated with any other adverse effects of MMF (except for 1 case of concomitant perianal ulcers[6]), and regression of the ulcers occurred within 7 to 10 days after discontinuation of MMF. By comparison, the reported interval between the initiation of MMF therapy and the formation of oral ulcers varies greatly, ranging from 1 week to 3 years. Notably, each of our three cases mirrored this pattern of clinical findings: oral ulcers developed within five to ten months of beginning MMF therapy, presented without the emergence of other adverse effects of MMF, and demonstrated dramatic improvement four to seven days after discontinuation of the drug.

Two mechanisms have been proposed to explain the association between MMF and oral ulcers. The first, and perhaps most likely, is a direct MMF-induced cytotoxicity on oral mucosa. This hypothesis is substantiated by the observation that in each reported case of MMF-associated ulcers (including the 3 published in this case series), both the size of the ulcers and their associated pain and odynophagia

markedly diminished immediately after the discontinuation of MMF therapy, suggesting a direct toxigenic relationship between the 2. Moreover, a case report published by Miquel et al[11] describing the association of oral ulcers and mycophenolate sodium (an enteric-coated, delayed-release formulation of MMF) in a patient with systemic lupus erythematosus documented the abrupt recurrence of the patient's oral ulcers several days after she was rechallenged with mycophenolate sodium, further corroborating the direct toxicity hypothesis.

Second, some have posited that the association between MMF and oral ulcers may be owing to viral infection secondary to immunosuppression. Although some empirical evidence for this hypothesis does exist, all viral cultures reported in the literature, including our cases, have been negative, and attempts to discontinue other immunosuppressive agents before discontinuing MMF have not successfully resolved patients' oral lesions.[8] The association between MMF-induced ulcers and viral infection is thus tenuous at best.

Regardless of the mechanism underlying mucosal damage, it is clear that an association exists between MMF and oral ulcers. In particular, recipients of solid organ transplants seem to be especially susceptible to the development of such ulcers. A possible explanation for the increased incidence of MMF-induced ulcers in these patients is that plasma levels of MMF have been found to increase dramatically when MMF is combined with certain additional immunosuppressive drugs, most notably cyclosporine.[14] In patients maintained on both medications—a frequent combination in transplant recipients—plasma drug concentrations of MMF may thus be much higher than initially anticipated, predisposing these patients to the development of oral ulcers. This explanation may also underlie the increased incidence of oral ulcers in transplant patients on a combination of MMF and sirolimus compared with those on MMF and tacrolimus.[10] Although plasma levels of MMF are not routinely assessed in hospitalized patients and are thus unfortunately not reported in any of the published cases series (including this one), limited pharmacologic data do support the assertion that elevated plasma levels of MMF may play a role in the development of oral ulcers in transplant recipients. MMF levels may therefore represent a useful adjunctive laboratory test to help confirm the diagnosis in patients with suspected MMF-induced oral ulcers.

Although the precise mechanism has yet to be elucidated, an association exists between MMF and the development of oral ulcers, especially among solid organ transplant recipients. MMF-induced aphthae should thus be added to the differential diagnosis of oral ulcerations in the immunocompromised host, and discontinuation of MMF should be considered in a patient with refractory oral ulcers and a negative workup for other etiologies.

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