Oral Ulcers Produced by Mycophenolate Mofetil in Two Liver Transplant Patients

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ABSTRACT

Oral ulcers are a frequent problem in transplant medicine. It is important to consider infectious etiologies, exacerbated by the immunosuppressive treatment, but other etiologies are also possible, like adverse drug reactions. Mycophenolate mofetil (MMF) is an immunosuppressive medication that has been used in combination with calcineurin inhibitors and steroids. Reports of renal transplant patients with oral ulcers related to MMF have appeared lately and herein we have described 2 cases in liver transplant patients. Their oral ulcers resolved quickly after suspension of the medication. Our 2 cases in liver transplant patients represented a unique setting for this type of complication.

ORAL ULCERS, a frequent problem in medicine, are sometimes signs of gastrointestinal diseases. Within their etiology, they vary from small, local traumas to malignant or systemic diseases. Special care is needed in transplant patients, because it is necessary to consider infectious etiologies, exacerbated by the immunosuppressive treatment, as well as adverse reactions to the medications. Mycophenolate mofetil (MMF) is an immunosuppressive medication that has been used in combination with calcineurin inhibitors and with steroids. Its adverse effects are mainly gastrointestinal dysfunction, leukopenia, and increased viral infections. There are reports of patients with oral ulcers related to MMF, but the 2 liver transplant patients with oral ulcers were unique. The cases resolved quickly after suspension of the medication.

CASE 1

The first patient was a 60-year-old woman with a history of type 2 diabetes mellitus and chronic arterial hypertension. In May 2003, she displayed spontaneous bacterial peritonitis and hepatic encephalopathy. The liver cirrhosis was probably secondary to nonalcoholic steatohepatitis (Child B), complicated by portal hypertension, esophagic varices, portal gastropathy, and ascites. The laboratory tests highlighted cytomegalovirus (CMV) IgG positive; toxoplasmosis IgG positive 1:16; and Epstein-Barr virus (EBV) IgG positive. She was awaiting liver transplantation.

In June 2005, orthotopic liver transplantation (OLT) was performed. She began taking methylprednisolone and cyclosporine (CsA). When she presented with an acute rejection, she was prescribed MMF 1 gram bid. Five days after MMF was initiated, ulcerated lesions with a whitish bottom appeared on the hard palate and tongue (Fig. 1). For these lesions she started empirically taking acyclovir (400 mg qid) plus amoxicillin (500 mg qid). Due to the persistence of the oral ulcers, it was decided to suspend MMF, maintaining CsA and prednisone. The oral ulcers disappeared 5 days after MMF suspension (Fig. 2). CsA (100 mg bid) was continued, plus 10 mg of prednisone every day.

CASE 2

The second patient was a 31-year-old woman who gave birth to twins 11 months prior without complications, and regularly took acetaminophen and piroxicam olamine for polyarthralgias. By the middle of July 2005, she showed symptoms of asthenia, jaundice, and choluria, followed by lapses in consciousness. In August, she was hospitalized in Copiapó, with subacute liver failure and hepatic encephalopathy G III. Immunological tests showed hepatitis A virus (HAV) IgM negative, hepatitis B surface antigen (HBsAg) negative, hepatitis C virus (HCV) negative, rheumatoid factor (RF) negative, rapid plasma reagin (RPR) negative, antimitochondrial antibodies (AMA) negative, and anti-smooth muscle antibodies (ASMA) positive 1/40. On September 2, we performed a treatment with the molecular adsorbent recirculating system (MARS). On September 3, an OLT was performed and she began methylprednisolone and CsA. She also was prescribed

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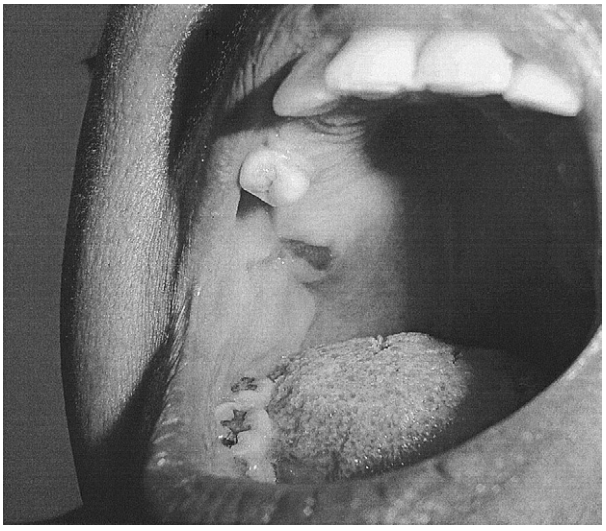

Fig 1. Case 1 before MMF discontinuation.

gancyclovir and imipenem plus vancomycin, due to methicillin-resistant *Staphylococcus aureus* (MRSA) in a quantitative culture of tracheal secretions.

On September 9, she developed biliary stenosis from choledochal kinking that required endoscopic retrograde cholangiopancreatography (ERCP) and stent installation. MMF (500 mg every 8 hours) was begun. On a routine examination, oral (labial) ulcers appeared, secondary to MMF (Fig 3). Its suspension was implemented and we began azathioprine (50 mg) plus prednisone (15 mg) plus CsA (150 mg every 12 hours). In the transplant clinic 1 week after suspending MMF, we verified complete disappearance of oral ulcers (Fig 4).

DISCUSSION

Oral ulcers induced by drugs are well known, but are unfortunately paid little attention, and the underlying mechanisms are unknown. It is critical to have the details of medications to be able to attribute the oral ulcers to an adverse drug reaction, especially when they are treatment-resistant, or when their cause is unknown. It is also important to define when the ulcerations began or if they worsened de novo upon an increased dosage. Some patients with drug-induced oral ulcers improve with local steroid treatment, but the definitive treatment relies on drug suspension.[1]

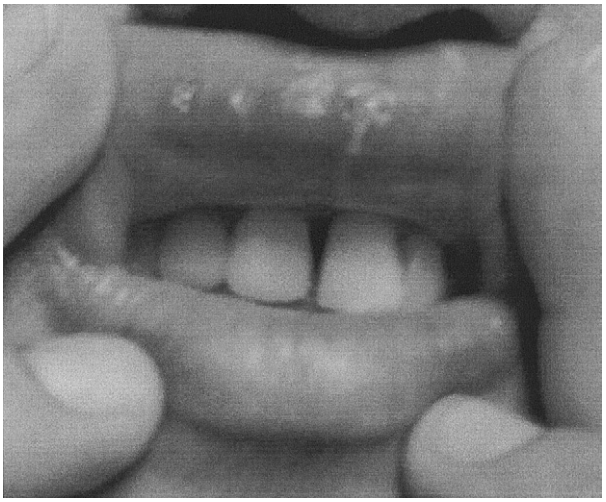

Fig 3. Case 2 before MMF discontinuation.

Our 2 cases have the particularity of being liver transplant patients. In our revision, we did not find any other cases of oral ulcers provoked by MMF in liver transplant patients. In both cases, previous treatment with antibiotics and acyclovir produced no response, whereas a quick clinical response was observed after MMF suspension. Due to the absence of added symptoms and fever, in addition to the knowledge of cases of oral ulcers and MMF in renal transplant patients, we opted to therapeutically test suspension of the suspicious drug.

In the last few years, reports of oral ulcers provoked by MMF in renal transplant patients have appeared. In one of

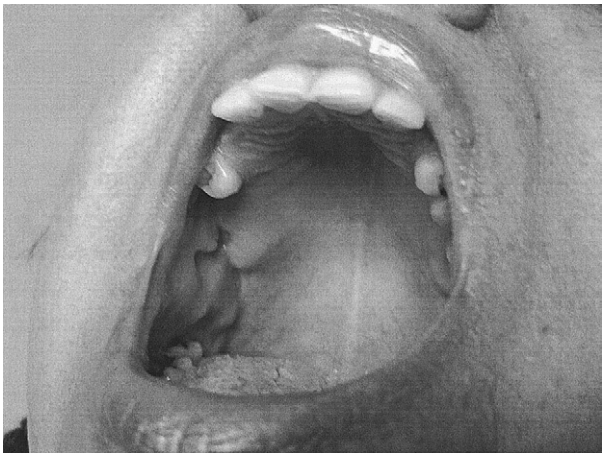

Fig 2. Case 1 after MMF discontinuation.

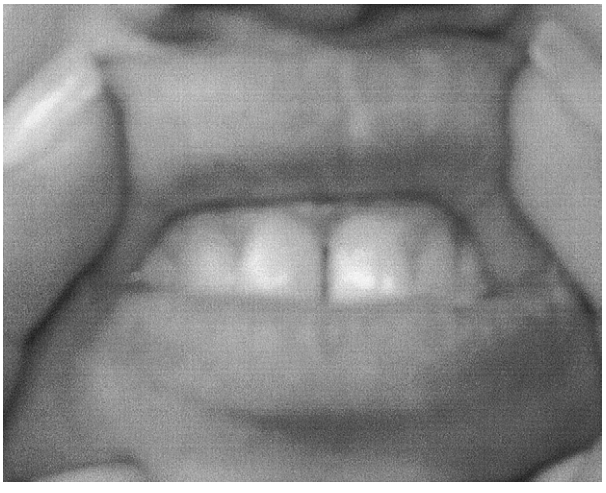

Fig 4. Case 2 after MMF discontinuation.

the first cases described by Garrigue et al,[2] the possibility of viral infectious causes was discarded by means of serological tests and PCR of biopsy materials. The patient's oral ulcers improved after the suspension of MMF. The authors concluded that the exact mechanism of the gastrointestinal toxicity of MMF is unknown, and that given the absence of fever and the quick improvement of the ulcers after its suspension, it was more likely due to a direct toxic damage on the gastrointestinal mucosa than a bacterial/viral proliferation induced by the immunosuppression[2], as was suggested in our 2 cases.

In a prospective, randomized, multicentric trial with renal transplant patients, van Gelder et al[3] sought to reduce the toxicity of the calcineurin inhibitors in a group of patients being treated with tacrolimus and MMF by a change to sirolimus and MMF. The study should have been suspended prematurely due to the appearance of 9 cases of painful oral ulcers in the experimental group. No ulcers were seen in the control group that maintained tacrolimus and MMF. The patients had been under treatment with MMF for 1 year before the study was initiated and they had never shown any oral ulcers. There was no change in the MMF dosage. The authors postulated that the incidence of oral ulcers was caused by MMF, due to an increased mycophenolic acid (MPA) trough level after the change from tacrolimus to sirolimus. It is known that higher MPA trough levels exist in patients treated with tacrolimus/MMF than in patients treated with CsA/MMF.[4] Other studies by Smak Gregoor et al[5,6] have clearly demonstrated that CsA diminishes MPA trough levels, which was corroborated in an experimental study.[7] It was postulated that the sirolimus coadministration resulted in a MPA concentration comparable to that of tacrolimus coadministration. For that reason, sirolimus coadministration, without a change in MMF, was the probable triggering factor. The antiproliferative effects and overgrowth factors of sirolimus have been associated with a higher prevalence of wound infections and a slowing in their scarring. This observation suggested their responsibility in the occurrence of mucous ulcers; the authors thought that sirolimus was possibly not the initiator of the phenomenon, but rather a hinderer of its repair.

In a work by Apostolou et al,[8] a renal transplant patient had oral ulcers that were attributed to MMF since they improved after its suspension. Infections by EBV, herpes simplex type 1 and 2 viruses, chicken pox virus, zoster, and CMV were discarded by means of serology and biopsy.[8]

Other etiologies in the genesis of the oral ulcers exist: (1) traumatic; (2) viral (herpes simplex type 1 and 2 viruses, EBV, CMV, human herpes virus 8, human immunodeficiency virus); (3) bacterial infections (acute necrotizing ulcerative gingivitis, *Treponema pallidum*, *Mycobacterium* infection); (4) fungal infections (*Candida, Aspergillus fumigatus, Histoplasma capsulatum*); (5) idiopathic causes (recurrent aphthous stomatitis, minor type, major type, and herpetiform type); (6) ulcers related to systemic diseases (gluten-sensitive enteropathy, dermatitis herpetiformis and related diseases, Crohn's disease and related disorders, ulcerative colitis, and others such as necrotizing sialometaplasia of bulimia nervosa); (7) dermatological diseases (lichen planus, pemphigus, pemphigoid, epidermolysis bullosa); (8) hematological diseases (oral ulcers related to iron deficiencies, neutropenia, and opportunistic viral infections), (9) malignancy (oral squamous cell carcinoma, non-Hodgkin's lymphoma, Kaposi's sarcoma, salivary gland malignancy, metastasis); and (10) adverse drug reactions (liquenoid drug reactions, erythema multiforme, pemphigus, lupus, pemphigoid, drug-induced neutropenia/anemia, drug-induced mycoses, and others).[9]

In conclusion, oral ulcers can have multiple etiologies, especially in transplanted patients, highlighting adverse drug reactions, given the multiple drugs taken by this type of patient. Our 2 cases had the particularity of being liver transplant patients, in whom this type of complication had not been found before. We believe their publication is important, as it will help outline the etiologies of oral ulcers in liver transplant patients, and allow physicians to act accordingly by suspending the suspicious drug.

REFERENCES

1. Field EA, Allan RB: Review article: oral ulceration—aetiopathogenesis, clinical diagnosis and management in the gastrointestinal clinic. Aliment Pharmacol Ther 18:949, 2003

2. Garrigue V, Canet S, Dereure O, et al: Oral ulceration in a renal transplant recipient: a mycophenolate mofetil-induced complication? Transplantation 72:968, 2001

3. van Gelder T, ter Meulen CG, Hené R, et al: Oral ulcer in kidney transplant recipients treated with sirolimus and mycophenolate mofetil. Transplantation 75:788, 2003

4. Zucker K, Rosen A, Tsaroucha A, et al: Unexpected augmentation of mycophenolic acid pharmacokinetics in renal transplant patients receiving tacrolimus and mycophenolate mofetil in combination therapy, and analogous in vitro findings. Transpl Immunol 5:225, 1997

5. Smak Gregoor PHJ, van Gelder T, Hesse CJ, et al: Mycophenolic acid plasma concentration in kidney allograft recipients with or without cyclosporine: a cross-sectional study. Nephrol Dial Transplant 14:706, 1999

6. Smak Greggor PHJ, De Sévaux RGL, Hené RJ, et al: Effect of cyclosporine on mycophenolic acid trough levels in kidney transplant recipients. Transplantation 68:1603, 1999

7. Van Gelder T, Klupp J, Barten MJ, et al: Comparison of the effects of tacrolimus and cyclosporine on the pharmacokinetics of mycophenolic acid. Ther Drug Monit 23:119, 2001

8. Apostolou T, Tsagalis G, Koutroubas G, et al: Mycophenolate mofetil and oral ulcerations. Transplantation 77:1911, 2004

9. Porter SR, Leao JC: Review article: oral ulcers and its relevance to systemic disorders. Aliment Pharmacol Ther 21:295, 2005