Apremilast for treatment of recurrent erythema multiforme

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Abstract

Recurrent erythema multiforme with oral involvement is therapeutically challenging. Apremilast has been used with success in resolving the oral aphthae of Behçet disease, prompting the use of the drug in patients with oral erosions from erythema multiforme. Three patients with oral erythema multiforme were given apremilast at doses of 30-60mg daily. Complete clearance of the lesions were observed in all three patients, including those refractory to other standard therapies. Apremilast may present an effective option for recurrent erythema multiforme for patients who have failed trials antiviral and immunosuppressive therapies.

Keywords: apremilast, otezla, erythema multiforme, recurrent erythema multiforme, EM, REM, Behçet's syndrome

Introduction

Erythema multiforme (EM) is an uncommon condition with unclear etiology that is found predominantly in young adults 20 to 40 years of age and characterized by targetoid lesions with concentric color variations, sometimes accompanied by oral, genital, or ocular mucosal erosions [1]. EM major refers to cases of EM with mucosal involvement, whereas EM minor refers to cases in the absence of mucosal involvement. Lesions normally appear over 3-5 days and resolve over 1-2 weeks, although severe cases may require up to six weeks for resolution [1]. The presentation of at least two episodes, typically an average of six episodes per year over the course of 6-10 years, constitutes recurrent EM (REM) in a subset of these patients [2]. These cases are most often associated with herpes simplex virus (HSV) and are treated with antiviral therapies. Immunosuppressive agents can be used in recalcitrant cases.

Case Synopsis

Patient 1 is a 21-year-old woman who presented with erosions in her mouth and a history of approximately six episodes per year of recurrent erosions on lips, tongue, and soft palate for over ten years. She had a previous diagnosis at age 6 of Behçet syndrome owing to recurrent oral and genital ulcers and joint pain and swelling (**Figure 1**A).

Acute episodes were successfully treated with prednisone. Trials of colchicine, dapsone, and hydroxychloroquine were unsuccessful. Serology was negative for HSV1/2. Lesions resolved completely

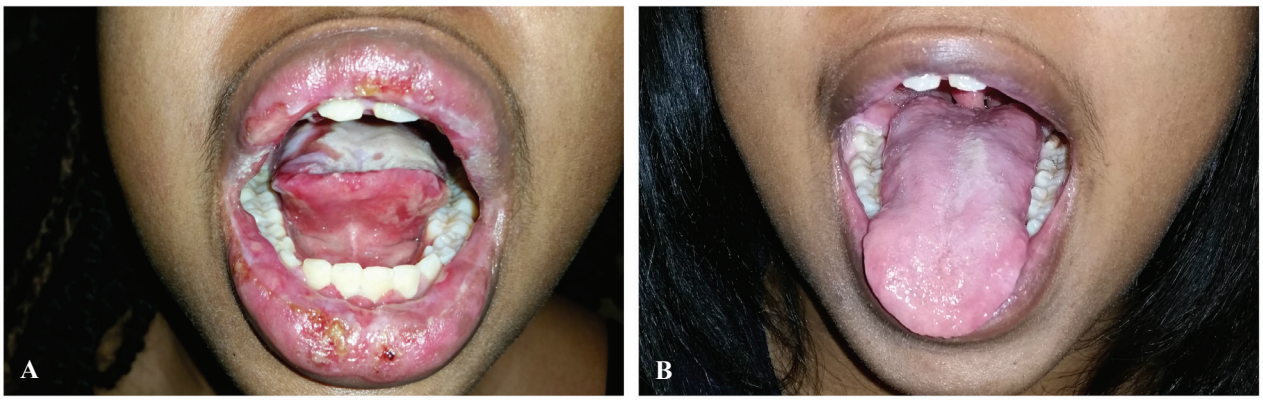

Figure 1. *A) Patient 1, Erythema multiforme oral lesions. B) Patient 1, Resolved lesions post apremilast.*

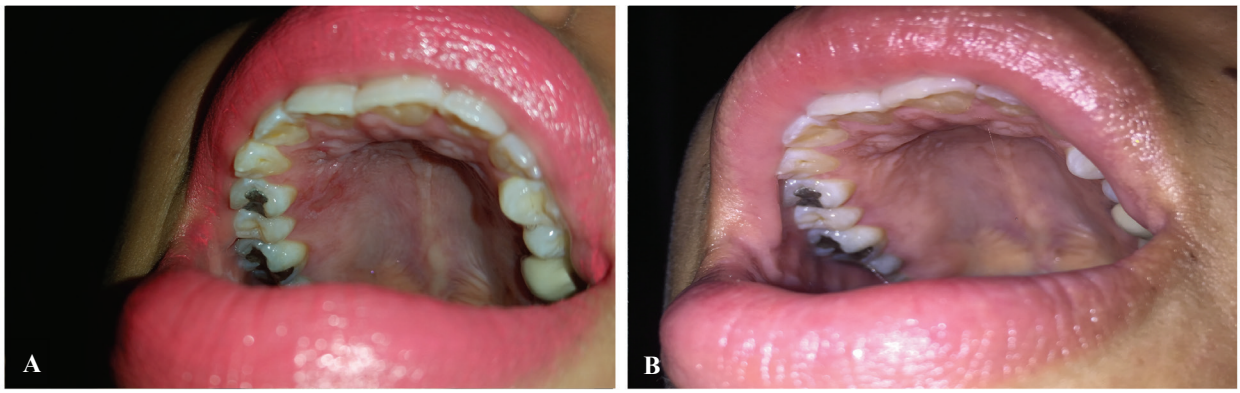

Figure 2. *A) Patient 2, erythema multiforme oral lesions B) Patient 2, resolved lesions post apremilast.*

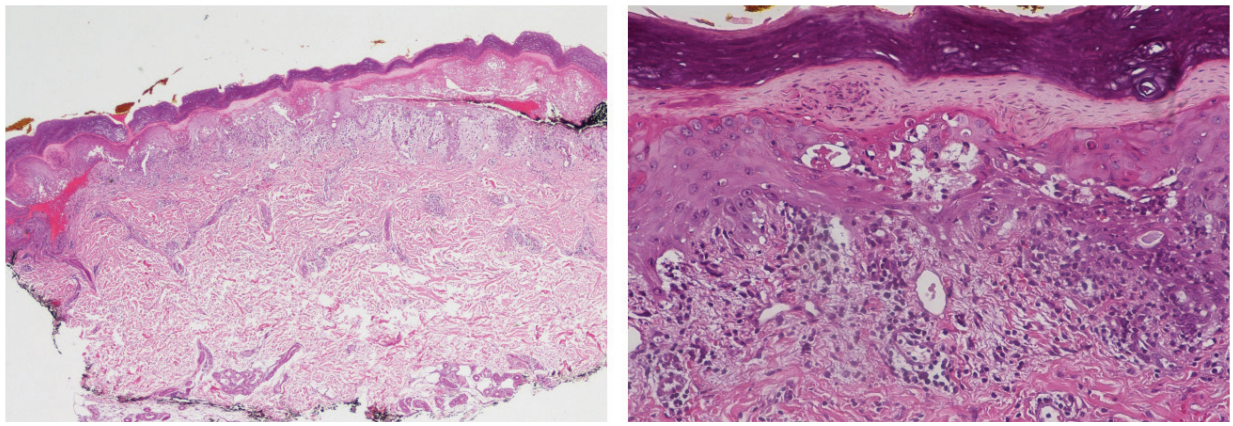

Figure 3. *A) Patient 2, biopsy revealing cell-poor interface dermatitis and characterized superficial epidermal necrosis. (H&E, 10x). B) Patient 2, biopsy revealing scattered dyskeratotic keratinocytes present throughout all layers of the epidermis. Numerous dyskeratotic keratinocytes are surrounded by lymphocytes along the dermal-epidermal junction. (H&E, 20x)*

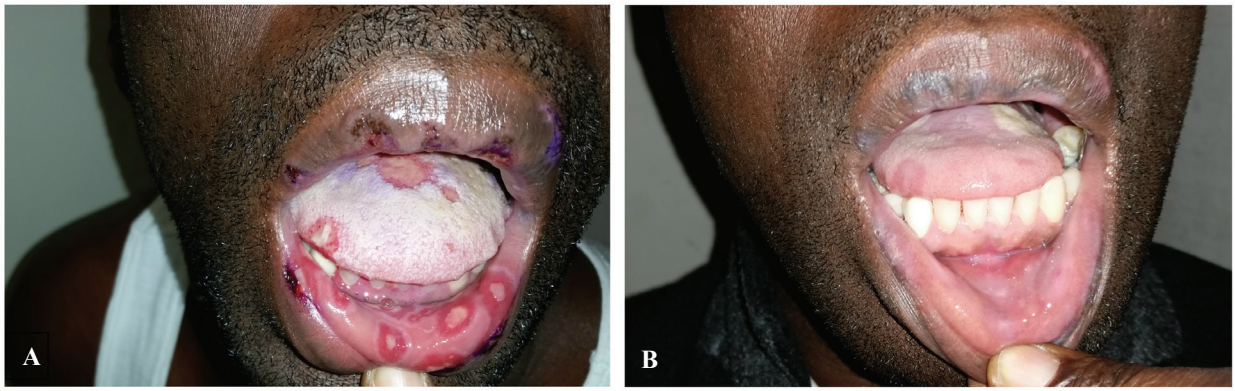

Figure 4. *A) Patient 3, erythema multiforme oral lesions. B) Patient 3, resolved lesions post apremilast.*

within one week after starting apremilast 30 mg PO BID with no recurrence for 6 months on therapy (**Figure 1**B).

Patient 2 is a 27-year-old woman (Patient 3 of Routt et al [3]) who presented with oral erosions of the mouth and on the hands (**Figure 2**A), consistent with EM on biopsy (**Figure 3**). These erosions were partly episodic for years and generally controlled through high dose, long-term treatment with prednisone. Serology was positive for HSV1 and 2. Trials of IVIG, rituximab, valacyclovir, and prednisone failed to resolve lesions. The lesions initially resolved with famcyclovir 500 mg PO TID; however, recurrence occurred after 3 months. Recurrence of the lesions temporarily responded to separate trials of etanercept 50 mg SC BIW and thalidomide 50 mg PO QHS, both with ultimate breakthrough. Apremilast 30 mg PO BID cleared the lesions for two months and with no recurrence (**Figure 2**B).

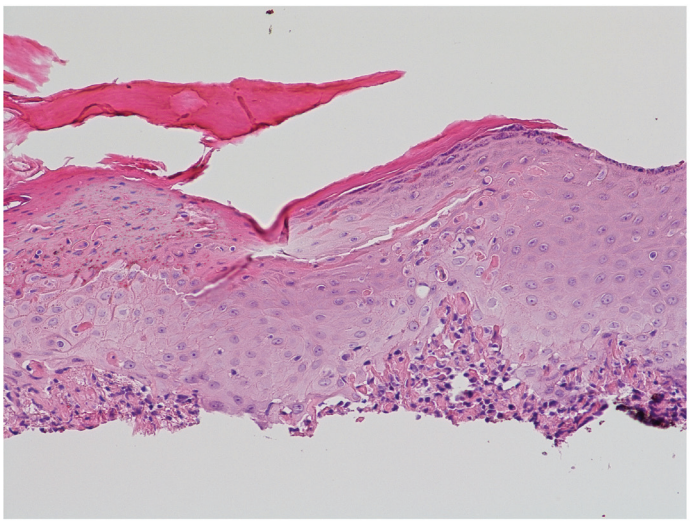

Figure 5. *Patient 4, biopsy revealing cell-poor interface dermatitis characterized by scattered dyskeratotic keratinocytes present throughout all layers of the epidermis. Numerous dyskeratotic keratinocytes are surrounded by lymphocytes along the dermal-epidermal junction. (H&E, 20x)*

Patient 3 is a 38-year-old man who presented with targetoid papules of the arms and hands and targetoid erosions of the lips and tongue with lip edema for four days with one previous occurrence (**Figure 4**A). The previous episode, approximately one-month prior, had lasted approximately two weeks and resolved with valacyclovir 1 g PO TID for 5 days. Treatment with valacyclovir provided no response at this time. HSV 1 and 2 IgG were negative when initially tested but HSV 1 IgG was positive on secondary testing. Biopsy confirmation was not performed. He completed a two week course of apremilast 30 mg PO BID and cleared after four days without dose titration or tapering and has not experienced recurrence to date (**Figure 4**B).

Patient 4 is a 6-year-old boy who presented to our pediatric emergency room with oral erosions and conjunctival injection consistent with erythema multiforme major upon biopsy (**Figure 5**).

HSV and mycoplasma studies were negative. He had one dose of ibuprofen prior to the onset of symptoms but did not take any other new medications in the preceding weeks. He was febrile but otherwise well. Two years prior to presentation, he was hospitalized with similar symptoms in the setting of a positive mycoplasma IgM and a new antibiotic, cefdinir. His rash at that time responded to intravenous immunoglobulin (IVIg). He was started on oral prednisone 1 mg/kg/day, but his symptoms worsened, and he developed swelling and hemorrhagic crusting of his lips (**Figure 6**A). He was subsequently treated with IVIg 2 g/kg divided over 3 days and one week of cyclosporine 5 mg/kg/day divided twice daily without improvement. He continued to have significant pain and intermittent bleeding from his oral mucosa and lips. He was unable to tolerate PO intake and required nasogastric tube feeds. At this time, a decision was made to initiate treatment with apremilast. On day one, he was given 10 mg PO BID. This was titrated up to 15 mg PO BID the next day and the following day to a final dose of 45 mg daily (30 mg PO in the morning and 15 mg PO at bedtime). His symptoms gradually began to improve. Two weeks after initiating treatment with apremilast, the swelling and hemorrhagic crusting of his lips had resolved and, except for one small erosion on his inner lower lip, his oral mucosa had healed as well (**Figure 6**B). He tolerated apremilast well without any headaches, abdominal pain, or diarrhea.

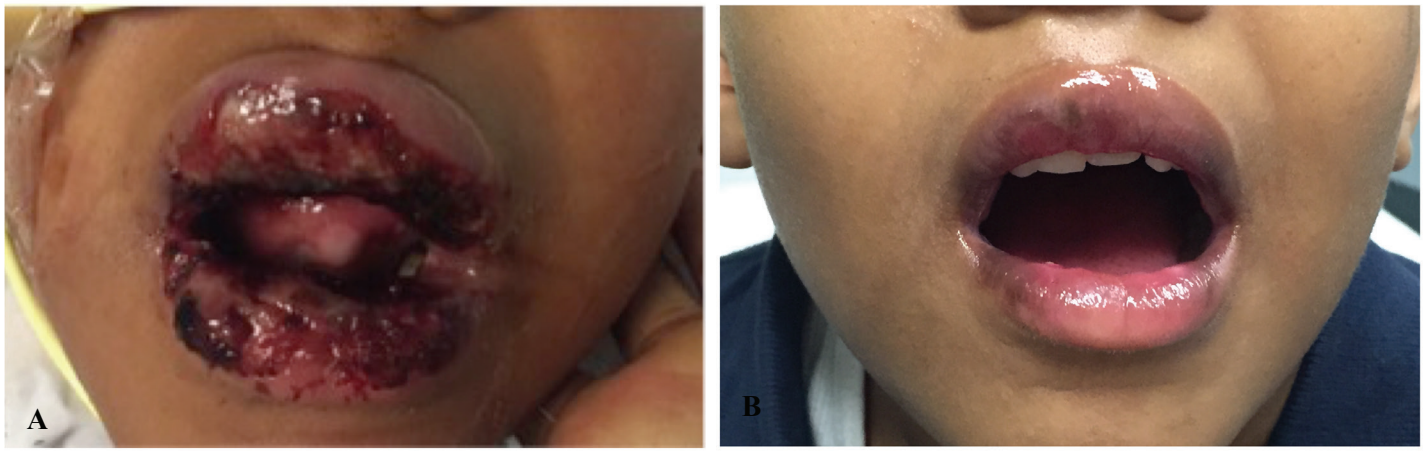

Figure 6. *A) Patient 4, erythema multiforme oral lesions. B) Patient 4, resolved lesions post apremilast.*

Case Discussion

The etiology of EM is not fully understood. However, onset is most commonly associated with infection, most commonly by herpes simplex virus (HSV) type 1 (less commonly type 2), constituting approximately 90% of cases of EM [4]. Patients with idiopathic EM may have sub-clinical HSV infection, which may be detected through PCR of skin biopsy specimens [4]. Currently, continuous antiviral therapy for six months has been demonstrated as the most effective first-line treatment of REM regardless of whether or not HSV is the precipitating factor [5]. Recommended treatments include acyclovir, valacyclovir, and famciclovir, and are most successful when the HSV association is clear and treatment begins at the onset of HSV flare [2, 4, 5]. Patients that are unresponsive to antiviral therapy may require treatment with immunosuppressive or immunomodulating agents. Treatments that have been used with variable success include azathioprine, prednisone, dapsone, mycophenolate mofetil, intravenous immunoglobulin, hydroxychloroquine, thalidomide, cyclosporine, and rituximab [2, 4, 6].

We found that treatment with apremilast was both effective and tolerable for four patients with REM with mucosal involvement. Although the safety and effectiveness of apremilast in patients less than 18 years of age have not been established thus far, patient 4 was able to tolerate apremilast at a dose of 1 mg/kg. In prolonged cases of REM in which antiviral and immunosuppressive agents fail, apremilast may be an effective option for recurrent erythema multiforme.

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