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Bilateral punctate keratitis and hurricane keratopathy following apremilast therapy

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ABSTRACT

Purpose: To report a unique case of bilateral punctate keratitis consistent with hurricane keratopathy during apremilast therapy.

Observations: A 49-year-old female presented with severe, painful, bilateral, punctate keratitis following five months of apremilast therapy. The past ocular history was noncontributory. The past medical history included psoriasis refractory to topical corticosteroids. The patient subsequently received systemic apremilast therapy and noted improvement in her psoriatic rash. Five months later the patient presented to an outside eye care provider complaining of three weeks of progressive photophobia associated with pain and redness in both eyes. On examination, the patient had decreased visual acuity with diffuse conjunctival injection and punctate epithelial erosions in a whorl-like pattern in both eyes. The remainder of the ophthalmic exam was unremarkable. The patient was started on topical moxifloxacin drops, erythromycin ointment, and preservative free artificial tears, but did not improve. Apremilast was then discontinued and topical prednisolone was added once per day. Ten weeks after discontinuation of apremilast and topical steroid therapy, the patient had recovered normal vision with an intact and normal corneal epithelium.

Conclusions and Importance: This is the first case report of cornea epithelial keratitis resembling hurricane keratopathy associated with apremilast treatment and should be recognized as a possible side effect of therapy with this class of drug.

1. Introduction

Apremilast (Otezla®) is an orally administered, small molecule inhibitor of phosphodiesterase 4 (PDE4) used to treat nail, scalp, and palmoplantar psoriasis.[1] Apremilast inhibits intracellular degradation of cyclic adenosine 3′,5′-monophosphate (cAMP), resulting in increased intracellular cAMP in cells expressing PDE4. This reduces expression of pro-inflammatory mediators and increases expression of anti-inflammatory mediators. These effects provide apremilast with an anti-inflammatory mechanism of action.[2]

Although effective in the treatment of psoriasis, apremilast has been associated with several notable side effects. The most frequent of these are nausea and diarrhea within the first fourteen days of starting therapy, resolving in most patients within twenty-eight days.[3,4] Depression and suicidal ideations have also been reported with use of apremilast.[5]

We present a case of bilateral epithelial keratopathy resembling hurricane keratopathy during apremilast therapy. Evaluation for alternative etiologies was negative, and we suggest that apremilast was most likely the underlying cause of the keratopathy. After a review of the English language ophthalmic literature we believe this case to be unique.

2. Case report

A 49-year-old soft contact lens wearing female presented complaining of severe pain in both eyes following five months of apremilast therapy. Past ocular history was noncontributory other than use of daily soft contact lenses and appropriate contact lens hygiene. Past medical history included psoriasis involving the hands and feet with associated joint pain refractory to topical betamethasone and triamcinolone. In December of 2021, the patient initiated apremilast therapy and three months later, in March of 2022, she noted improvement in her psoriasis symptoms.

In May of 2022, the patient presented to an outside eye care provider with complaints of three weeks of progressively worsening photophobia associated with pain and redness in both eyes (OU). At this time the

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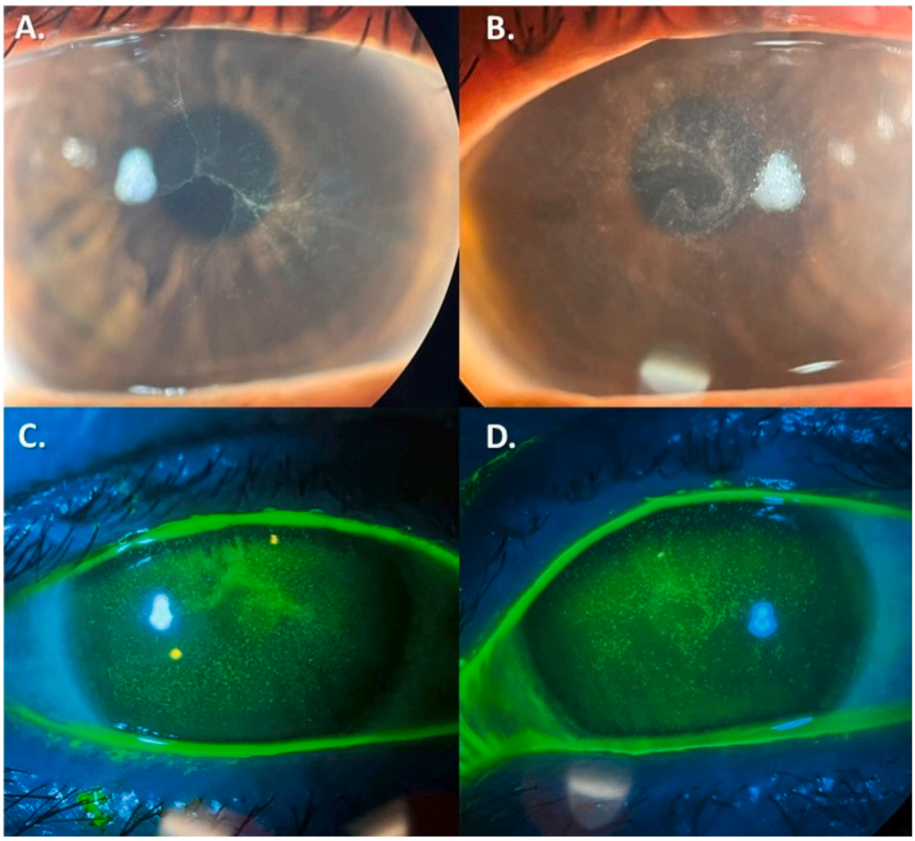

Fig. 1. Slit lamp photographs at initial presentation. In (A) and (B), representing OD and OS respectively, a whorl-like pattern of opacity is seen in each cornea. Subsequent staining with fluorescein as shown in (C) and (D), representing OD and OS respectively, highlights these distributions of dense, punctate epithelial erosions in each eye.

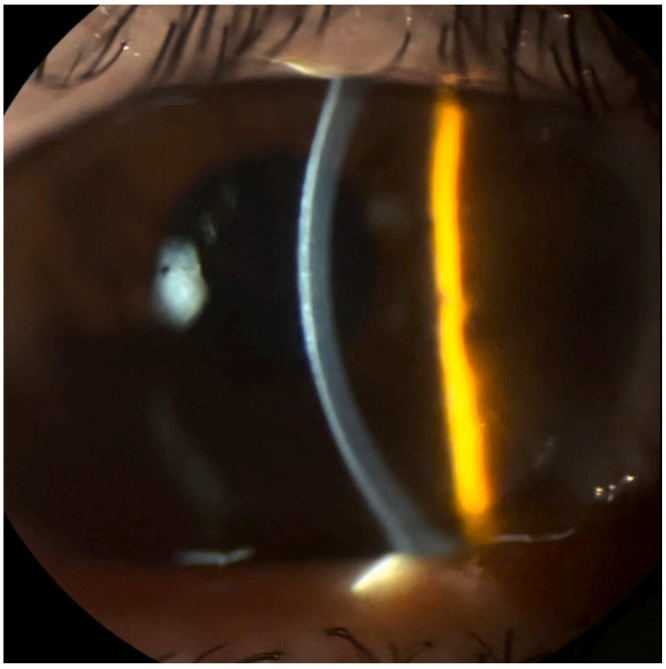

Fig. 2. Slit lamp exam with slit beam demonstrating level of involvement limited to epithelium without associated stromal involvement.

patient stated she was unable to drive due to her symptoms and perceived decrease in vision with additionally inability to wear her contact lenses for any length of time. On the initial ophthalmic examination at our facility she demonstrated an uncorrected visual acuity of 20/70 in the right eye (OD) and 20/60 in the left eye (OS), with pinhole correction to 20/60 and 20/50 respectively. The patient's pupils were reactive bilaterally without anisocoria or a relative afferent pupillary defect and her intraocular pressures (IOPs) were 22 mm Hg OD and 23 OS. Slit lamp examination demonstrated diffuse conjunctival injection, and a whorl-like pattern of dense, punctate, corneal epithelial erosions OU (Fig. 1). Corneal sensation was intact bilaterally on testing using the cotton wisp method, and the anterior chamber was without cell or flare. The remainder of the ophthalmologic and funduscopic exam was unremarkable. The patient was initially prescribed topical moxifloxacin eye drops, topical ophthalmic erythromycin ointment qHS, preservative-free artificial tears, oral valacyclovir 1 g TID, and told to discontinue any contact lens use. Three days later, given no significant improvement or worsening, the patient was referred to our cornea specialists for further evaluation and treatment.

At one week after the initial visit, the patient's examination demonstrated whorl-like changes in the corneal epithelium without obvious stromal involvement and no associated infiltrate suggestive of infectious etiology (Fig. 2). Her topical antibiotics at this time were discontinued, she was continued on her preservative-free artificial tears (carboxymethylcellulose 0.25%) that she was using approximately every 2 h, and she was started on topical prednisolone 1% at once a day. After discussing with the patient the possibility of apremilast being related to her eye condition she was dechallenged and re-evaluated four days later. Her exam was notable for partial resolution of the keratopathy in the periphery with only some residual central findings indicating a positive dechallenge.

Four weeks after discontinuation of apremilast the patient's condition had improved significantly and she was able to resume driving while only continuing preservative-free artificial tear use and use of the

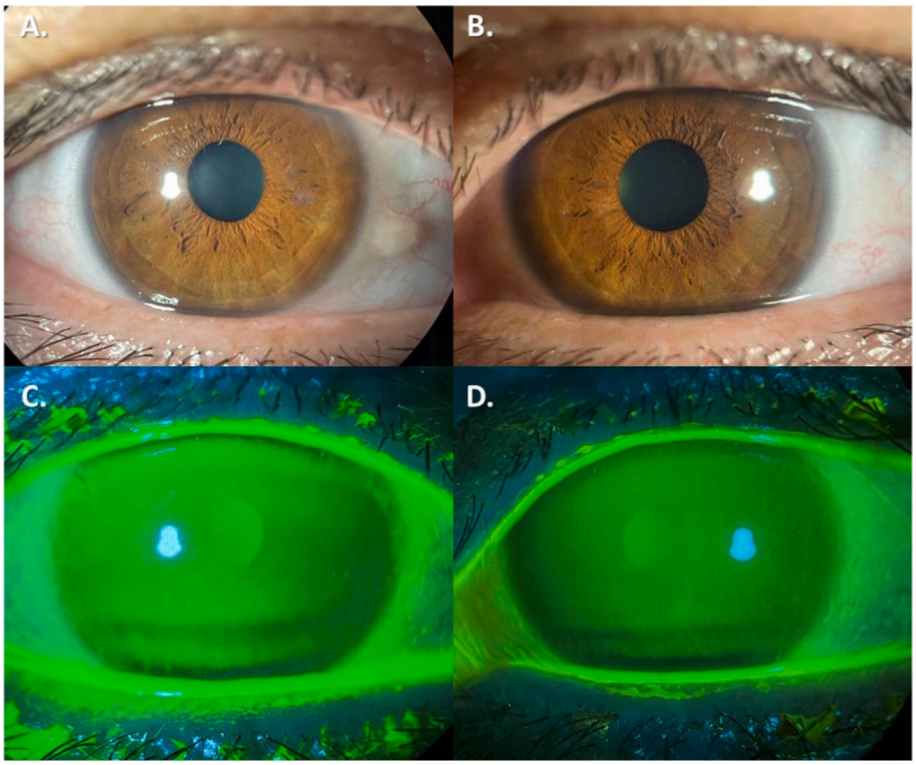

Fig. 3. Slit lamp photographs at follow-up examination 10 weeks after discontinuation of apremilast therapy. (A and C: OD; B and D: OS). Both corneas were free of opacity (A and B), and were negative for fluorescein staining (C and D).

topical prednisolone only once daily. By July of 2022, ten weeks after discontinuation of Apremilast, the patient's symptoms had fully resolved, and the patient discontinued the prednisolone while continuing to use preservative-free artificial tears (Fig. 3). After several months of remission the patient reattempted apremilast therapy at a lower dose per her Rheumatologist, experienced repeat bilateral eye discomfort, and immediately discontinued therapy indicating a positive rechallenge even at a lower dose.

3. Discussion

We present a case of severe, bilateral, corneal epithelial erosions with a whorl-like pattern (hurricane keratopathy), occurring 5 months after initiation of apremilast therapy for psoriasis. All findings resolved within 10 weeks of starting preservative-free artificial tears, topical prednisolone, and discontinuation of apremilast. Cases of punctate keratopathy have been previously described following use of the chemotherapeutic and immunosuppressive medications afatinib, cetuximab, and infliximab,[6–8] but not previously with apremilast or the other FDA-approved PDE4 inhibitors, roflumilast and crisaborole.

As with other cases of systemic drug-associated corneal disorders, a mechanism for corneal epithelial involvement, if due to apremilast, is unclear. Given the findings of hurricane keratopathy rather than vortex keratopathy as defined by the whorl-like pattern highlighted by use of fluorescein, these findings suggest an issue with epithelial cell cohesion in the setting of migration. Indirectly, there may be a possible component of high cell turnover with associated migration due to possible genotoxic effect of the drug on limbal progenitor cells which has been observed in a mice model.[9] Alternatively, rather than a toxic effect, it may be that the use of apremilast causes a yet unclear change to the proliferation or remodeling of corneal epithelium leading to these findings during migration of the cells. One study in a rat model demonstrated a significant improvement in wound healing and inflammatory mediator control in the use of apremilast through the use of a nanoemulsion gel.[10] As wound healing involves both proliferation and remodeling as well as complex control of inflammation, further studies into apremilast may help further our understanding of the corneal epithelium.

Although a recent review of ocular side effects of antirheumatic medications found no prior reports of ocular toxicity associated with apremilast,[8] there have been reports of epiphora associated with its use.[11] As our patient presented with her corneal findings, it could be possible that some patients with increased tearing may have corneal epithelial changes suggestive of apremilast-related keratopathy rather than isolated epiphora. Performing a detailed fluorescein exam on these patients in the future for any ocular complaint may help us better diagnose and understand future ocular findings in these patients.

4. Conclusions

Apremilast may induce a corneal epithelial keratopathy (hurricane keratopathy), which should be recognized as a possible side effect of therapy. Ophthalmologists, optometrists, dermatologists, and general practitioners should be aware of the possibility of keratopathy with use of apremilast. Although likely rare, keratopathy should be added to the list of potential side effects of apremilast therapy, and patients treated with apremilast or other PDE4 inhibitors should be referred to an ophthalmologist in the case of any ocular complaints.

Authorship

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article.

Patient consent

Verbal consent by patient has been obtained. This report does not contain any personal identifying information.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

Logan Wolfel, Jimena Franco, Thomas Bradford Gillette, James Chodosh, and Alexander Davis declare that they are the sole contributors to this manuscript.

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