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Case report

Trichiasis and dry eye syndrome in two patients on novel fibroblast growth factor receptor inhibitor therapies

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ABSTRACT

Purpose: Present two patients on two different novel FGFR inhibitors who developed trichiasis with dry eye syndrome.

Observations: Two patients developed trichiasis and dry eye following FGFR inhibitor therapy. Treatments included artificial tears, lifitegrast or cyclosporine, and epilation as needed. One patient discontinued treatment with AZD4547 due to the severity of the ocular adverse effects.

Conclusions and Importance: Trichiasis has not yet been reported in patients receiving AZD4547 or INCB054828 treatments and may represent a rare adverse effect of these drugs. Continued research is necessary to determine whether there is a definite link between these FGFR inhibitors and the development of trichiasis.

1. Introduction

Fibroblast growth factors (FGF) and their receptors (FGFR1-4) are receptor tyrosine kinases (RTK) that play an important role as regulators of cellular functioning. Deregulation of the FGF signaling pathway has been implicated in many cancers, and agents targeted at deregulated FGF/FGFRs are therefore emerging as effective antineoplastic therapies.[1] AZD4547 and INCB054828 (pemigatinib) are two novel FGFR inhibitors that are generally well-tolerated,[2] but little has been reported regarding the adverse effects of these drugs due to their recent emergence.

Herein, we report two cases of trichiasis and dry eye syndrome in patients on AZD4547 or INCB054828, both of which are currently in active Phases I-III clinical trials. While dry eye has been previously reported as a possible adverse effect of AZD4547[2,3], there have been no cases of trichiasis reported in patients on either therapy to our knowledge.

1.1. Findings

1.1.1. Case 1 – AZD4547

A 72-year-old female initially presented with excessive bilateral tearing. She had recently finished two 21-day cycles of AZD4547 over six weeks for squamous cell carcinoma of the lung and was scheduled to receive her third cycle beginning the next day. She had no past history of dry eye or trichiasis. Examination was significant for 1+bilateral diffuse corneal punctate staining with fluorescein and decreased tear meniscus. At this time, administration of artificial tears was recommended. One week later, the patient returned with complaints of redness and gritty sensation in her eyes despite using artificial tears 6–8 times daily. Examination revealed several errant lashes, 4+bilateral diffuse corneal punctate staining with fluorescein, and decreased tear meniscus bilaterally. Prednisolone acetate ophthalmic suspension four times daily was initiated. Lifitegrast ophthalmic solution and punctal plugs were added the following month due to worsening trichiasis and dry eye symptoms and provided some improvement in her condition. However, the patient subsequently discontinued AZD4547 therapy due to the severity of her ocular adverse effects.

Three weeks after discontinuing AZD4547, the patient reported significantly improved symptoms. Examination revealed improved trichiasis with no lash touch and only trace corneal punctate staining with fluorescein. In a final encounter 14 weeks later, no misdirected lashes were observed and corneal punctate staining was unchanged.

1.1.2. Case 2 – INCB054828

A 69-year-old male initially presented with excessive bilateral

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tearing. He had received a cycle of INCB054828 six months earlier for adenocarcinoma of the gallbladder. He had no past history of dry eye or trichiasis. Bilateral 2+corneal punctate staining with fluorescein and severe bilateral, upper lid trichiasis with coiled, tortuous lashes was noted (Fig. 1). Epilation with jeweler forceps was performed, and aggressive lubrication with artificial tears and lifitegrast ophthalmic solution was initiated. However, the patient did not tolerate lifitegrast, which we replaced with 0.05% cyclosporine ophthalmic emulsion twice daily.

The patient's symptoms and exam findings gradually improved over the course of one year with continued artificial tear use and cyclosporine therapy as well as periodic epilation, and the patient was able to remain on INCB054828 therapy.

2. Discussion

Two patients enrolled in separate Phase II clinical trials for FGFR inhibitors both developed trichiasis and dry eye syndrome. A thorough review of the literature did not reveal previous reports of trichiasis in patients undergoing therapy with either agent, although four cases of dry eye were reported in patients taking AZD4547 and cases of dry mucus membranes have been reported with both AZD4547[2,3] and INCB054828.[4]

Due to the severity of her ocular adverse effects, the patient receiving AZD4547 therapy discontinued her treatments with AZD4547. Early recognition and management of ocular adverse effects in the setting of AZD4547 and INCB054828 treatments is therefore important for maintaining patient tolerance to these agents. The onset and resolution of trichiasis and dry eye symptoms were more rapid in the patient receiving AZD4547, beginning six weeks into treatment and resolving completely 14 weeks after discontinuing treatment. In contrast, the patient who received INCB054828 treatment presented with trichiasis and dry eye six months after finishing a cycle of INCB054828, and symptoms resolved slowly over the course of one year. It is possible that AZD4547 is associated with more rapid onset ocular adverse effects when compared with INCB054828, and providers should anticipate the need for supportive ocular therapies early in the course of treatment if necessary.

The pathogenesis of ocular adverse effects from various RTK inhibitors, including epidermal growth factor receptor (EGFR) inhibitors, is well-described.[5] To our knowledge, however, the mechanism of ocular toxicity from FGFR inhibitors has not been addressed. The literature does show that FGFR2 is expressed in developing corneal tissues during embryogenesis and appears to play an essential role in controlling cell proliferation and differentiation within the cornea.[6] Furthermore, corneal dysmaturation has been suspected in a number of patients exposed to the FGFR inhibitors ASP5878 and FPA144.[7] Therefore, we suggest that FGFR inhibition may predispose patients to corneal epithelial changes and subsequent dry eye syndrome due to dysmaturation and poor wound healing. Concerning ocular adnexal adverse effects, studies of other RTK inhibitors have implicated EGFR monoclonal antibodies as well as Bcr-Abl and c-Kit inhibitors in ocular adnexal disease due to expression of their respective receptors in the orbit, peri-orbit, lids, lashes, hair follicles, and capillary systems.[5] EGFR inhibitors have also been associated with ectropion and entropion.[5] It is possible that FGFR is also expressed in ocular adnexal tissues including eyelash follicles, and thus, inhibition of FGF signaling pathways could compromise the structure of eyelash follicles and predispose to trichiasis.

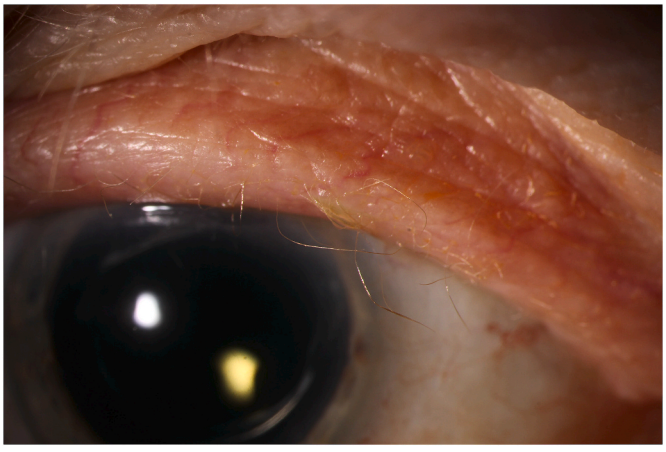

Fig. 1. Case 2, left upper lid demonstrating trichiasis with coiled and wire-like lashes.

3. Conclusions

Based on our findings, we recommend that providers be alert for symptoms of trichiasis in patients who are undergoing therapy with AZD4547 and INCB054828 for early detection. Management should include preservative-free artificial tears, lifitegrast ophthalmic solution or cyclosporine ophthalmic emulsion, and epilation as needed. Continued research with attention to ocular adverse effects is needed to determine whether there is a definite association between AZD4547 and INCB054828 and the development of trichiasis and dry eye syndrome.

Patient consent

These case reports were exempted by the Prisma Health - Upstate Institutional Review Board and Prisma Health – Upstate Privacy Office.

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Intellectual property

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

Research ethics

We further confirm that any aspect of the work covered in this manuscript that has involved human patients has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

Authorship

The International Committee of Medical Journal Editors (ICMJE) recommends that authorship be based on the following four criteria:

1. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
2. Drafting the work or revising it critically for important intellectual content; AND
3. Final approval of the version to be published; AND
4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Declaration of competing interest

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