Case Report

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Bilateral keratitis associated with afatinib therapy

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Abstract:

This case discussed a significant ocular side effect, bilateral keratitis, which could be induced by afatinib, an irreversible epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI). We explored the disease progression of a 52-year-old, stage IV nasopharyngeal carcinoma male patient, who was under afatinib treatment and had experienced progressive bilateral eye dryness and tenderness on increasing afatinib from 40 mg every other day to 40 mg daily. Clinical examination noted bilateral visual acuity reduction, diffuse superficial punctate keratopathy in the right eye, and a central epithelial defect in the left eye. Seidel test results were negative for both eyes, with no corneal infiltration, lagophthalmos, anterior chamber cell precipitation, or retinal lesion. Symptoms subsequently resolved after reducing the frequency of afatinib used, along with intensive ocular hydration. In summary, this case highlighted afatinib's potential link to bilateral keratitis, and early afatinib dose adjustment with supportive medication could significantly reverse the condition.

Keywords:

Afatinib, epidermal growth factor receptor-tyrosine kinase inhibitor, keratitis

Introduction

Afatinib, an irreversible epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI), is the first-line treatment for nonsmall-cell lung cancer (NSCLC) with EGFR mutation[1] and a promising combinatory therapy for metastatic nasopharyngeal carcinoma (NPC) with EGFR overexpression.[2] EGFR is distributed over corneal and periocular regions. EGFR-TKI inhibits the phosphorylation process required in corneal epithelial cell migration and proliferation;[3] therefore, it might damage the health of corneal epithelium. Given the rising use of afatinib and limited ophthalmological case reports,[4,5] we presented a case of bilateral keratitis, which was highly suspected to be secondary to the afatinib therapy. The aim is to increase awareness among oncologists and ophthalmologists regarding the need for vigilant monitoring of potential ocular side effects and early dose adjustment when a patient is on afatinib.

Case Report

A 52-year-old male with multiple bone metastases from stage IV NPC experienced tumor recurrence despite undergoing salvage treatment with cisplatin-fluorouracil (PF) and maintenance therapy with capecitabine (Xeloda). Hence, targeted therapy with afatinib (40 mg/day) and pembrolizumab (100 mg/month or 2 mg/kg/month) was initiated. Within 1 week of treatment, the patient developed multiple erythematous papules and plaques over his body and was diagnosed as a drug eruption related to TKI treatment. Consequently, the afatinib dosage was reduced from 40 mg/day to 40 mg every other day.

In view of the stable condition with tolerable side effects, the afatinib dosage was gradually increased back to 40 mg/day.

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Approximately 2 weeks after dosage adjustment, the patient reported progressive bilateral eye dryness and tenderness. No photophobia, tearing, or discharge was mentioned. The patient was then referred to the ophthalmic clinic where he denied prior ophthalmic problems, surgery, trauma, or contact lens use. There was no documented history of autoimmune disease or connective tissue disease. On examination, the patient's corrected visual acuity was 12/20 in the right eye and 6/20 in the left eye. Both eyes exhibited meibomian gland dysfunction and mild conjunctival congestion. Slit-lamp examination and fluorescent stain showed that the right cornea displayed a diffuse superficial punctate keratopathy (SPK), which was extended from the central to the lower half of the cornea, and the left cornea presented a 10 mm × 4 mm epithelial defect (ED) spanning from the central to the 6 o'clock direction [Figure 1]. The Seidel test yielded negative results for both eyes. The patient did not exhibit lagophthalmos or corneal infiltration in either eye, and his tear breakup time was not reduced. Both eyes displayed normal anterior chamber depth and clear aqueous humor. A dilated examination revealed a pinkish disc with a normal macula in both eyes. Considering the history of recent target therapy use, the initial impression was TKI-induced keratitis. Treatments included lubricant eye drops as needed, carbomer eye gel (Vidisic® Gel, GMBH) thrice daily, and prophylactic 0.5% levofloxacin eye solution (Cravit®, Santen) four times daily given the patient's immunocompromised status. Meanwhile, the patient consulted the dermatologist again for an acneiform eruption, which was also diagnosed as a drug eruption.

About 1-week posttreatment, the patient's corrected visual acuity continued to decline, 20/40 in the right eye and 20/200 in the left eye, and the extent of bilateral SPK had increased. Given the patient's immunocompromised state, bilateral herpes simplex virus (HSV) keratitis was suspected. The patient was treated with famciclovir 250 mg, three times a day for 14 days, along with hourly balanced salt solution (BSS) for intensive hydration.

Due to new eye symptoms and recurrence of skin side effects, the patient's afatinib dosage was adjusted back to 40 mg every other day. Approximately 1 week after reverting afatinib dosage, bilateral SPK had reduced in extent, but a 1.5 mm × 3 mm ED had developed in the right eye and another 1.5 mm × 2 mm ED had developed in the left eye [Figure 2]. Hence, famciclovir was continued for an additional 2 weeks, and prophylactic antibiotic levofloxacin eye solution at 0.5% was added four times daily. In addition to BSS, carbomer eye gel at 0.2% was introduced three times daily to further enhance lubrication.

After slightly over 2 weeks of afatinib dose adjustment and intensive lubrication, the patient's bilateral SPK and ED had resolved [Figure 3], with a marked improvement in dryness sensation.

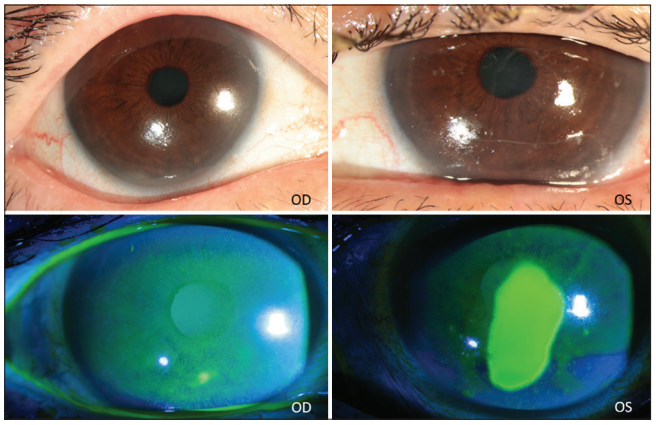

Figure 1: External eye photo of the patient after afatinib use, featuring a direct examination of bilateral corneas with and without fluorescein staining. (OD) Displays diffuse superficial punctate keratopathy at the cornea's central region. (OS) Exhibits a 10 mm × 4 mm epithelial defect (ED) spanning from the central to the 6 o'clock direction

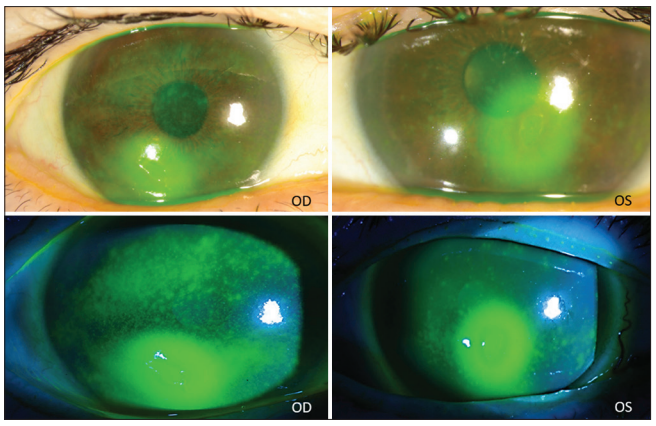

Figure 2: External eye photo of the patient 1 week after tapering afatinib. (OD) Showed reduced extent of superficial punctate keratopathy and a new 1.5 mm × 2 mm epithelial defect (ED) at 6 o'clock. (OS) Demonstrated a reduction in the initial ED size

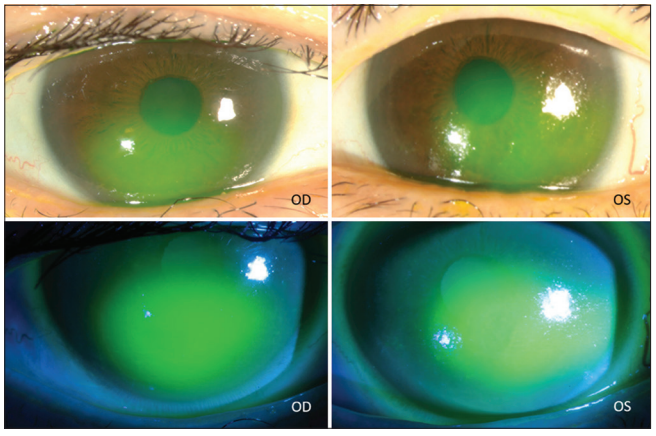

Figure 3: External eye photo of the patient 2 weeks after tapering afatinib. Significant resolution of bilateral superficial punctate keratopathy and epithelial defect in both eyes (OU)

Discussion

This case illustrated a patient who underwent treatment with afatinib and pembrolizumab and developed bilateral keratitis and EDs. Symptoms worsened with an increased afatinib dose but improved on dose reduction, while the pembrolizumab dosage remained constant. Before diagnosing TKI keratitis, the deterioration in the patient's cornea also raised suspicion of a superimposed HSV infection due to their immunocompromised status and reduced corneal sensitivity. Therefore, antiviral eye drops were administered. Eventually, bilateral corneal lesions resolved about 2 weeks after afatinib dose reduction.

EGFR is found in ocular and periocular tissues, encompassing the eyelids, eyelash follicles, meibomian glands, tear glands, conjunctiva, and cornea,[6] which would explain the side effects associated with afatinib on ocular tissues. On EGF binding to EGFR, it undergoes dimerization and autophosphorylation, allowing the corneal limbal epithelium, keratinocytes, and endothelium to migrate, proliferate, and grow.[7] Hence, EGFR-TKIs, which disrupt normal ocular homeostasis pathways,[8] prolong corneal epithelial wound repair by inhibiting cell growth and differentiation. Clinical presentations of EGFR-TKI-related ocular adverse events include dry eyes, blepharitis, conjunctivitis, ulcerative keratitis, uveitis, photophobia, and blurred vision.[5,9] Corneal surface impairment also increases the patient's vulnerability to opportunistic infection, including HSV. Notable EGFR-TKIs and their reported side effects were erlotinib, associated with persistent corneal erosion and infectious keratitis that resolved only after medication discontinuation;[10] gefitinib, posing the risk of corneal thinning, conjunctivitis, cataract, and uveitis;[11,12] and imatinib, exhibiting ocular toxicity similar to gefitinib with additional signs of eye edema.[13] Despite the reported incident rate of 0.8%, there is a scarcity of published case reports detailing preventive measures for ocular side effects associated with afatinib.[4] Hence, this case report aims to further discuss the impact of afatinib on the cornea and propose possible management strategies to minimize its ocular adverse events, especially bilateral keratitis.[4]

The increased utilization of afatinib, a second-generation EGFR-TKI, in the treatment of NSCLC and NPC may contribute to a growing incidence of EGFR-TKI-related keratitis. Afatinib demonstrated efficacy, precision, and fewer side effects in the treatment of NSCLC.[14,15] It also showed potential as a radiation sensitizer to enhance treatment for NPC.[16] In contrast to first-generation reversible EGFR-TKI such as erlotinib, gefitinib, and imatinib, irreversible inhibition of EGFR by afatinib had shown superiority in cancer treatment.[17,18] However, this advantage of irreversibility may result in more significant ocular adverse effects. The anticipated rise in afatinib use suggests a potential increase in the number of adverse ocular events.

Adjusting afatinib doses based on tolerability might not compromise therapeutic effectiveness.[19] According to the adverse event grading outlined in the National Cancer Institute's Common Terminology Criteria for Adverse Events version 3.0, grade 2 ocular dryness requires medical intervention, while grade 3 and above may necessitate surgical intervention or drug discontinuation.[20] In a recent study, Yang *et al*. reported that patients requiring afatinib dose reduction showed similar progression-free survival (>11 months) compared to those who did not.[19] This indicated that tolerability-guided dose adjustments might not compromise afatinib efficacy once the optimal dose is achieved. The use of a lower dose might also reduce adverse events associated with afatinib, resulting in lower treatment discontinuation rates. Yang *et al*.[19] identified that patients more likely to require dose reduction were those with lower body weight, older age, Japanese ethnicity, and female gender. However, this study did not recommend initial dose modification based on patient clinical characteristics, as an initial loading dose might still be essential. Further large-scale studies are needed to support this theory. Meanwhile, dose reduction appeared promising for mitigating afatinib-related ocular adverse events while enabling continued cancer treatment.

Afatinib-related ocular adverse events could be addressed by supporting medication without afatinib dose titration. Medications available in present reports included frequent hydration with preservative-free artificial tears, autologous serum eye drops, and lubricating ointments. It helped to facilitate corneal epithelial wound healing. The short-term use of corticosteroid and cyclosporine eye drops aimed to alleviate ocular discomfort and reduce inflammation, thereby preventing keratitis progression. The prescription of antiviral eye drops addressed potential superimposed infections. Punctal plugs could be considered if there are persistent aqueous-deficient dry eyes despite the use of hydration medication. In cases of severe ED, a bandage contact lens might be indicated to protect the cornea from the shearing effect of blinking.[9,13,21,22] While some proposed EGF eye drops as an alternative treatment for symptoms related to EGFR inhibitors,[23] it may not exhibit the same efficacy in cases like ours, where the patient was on the irreversible EGFR-TKI afatinib, as opposed to the patient in the referenced study who was using the reversible EGFR-TKI cetuximab. The effectiveness of EGF eye drops required further studies.

In conclusion, although there are medical treatments available that allow for the mitigation of adverse effects associated with afatinib, bilateral keratitis secondary to afatinib use can still pose significant threats to vision and diminish a patient's quality of life. Hence, early ophthalmologist monitoring and intervention is essential for patients with ocular symptoms and on afatinib use.

Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that his name and initials will not be published, and due efforts will be made to conceal his identity, but anonymity cannot be guaranteed.

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Conflicts of interest

Dr. Chi-Chin Sun, a section editor at *Taiwan Journal of Ophthalmology*, had no role in the peer review process of or decision to publish this article. The other authors declared no conflicts of interest in writing this paper.

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