Tyrosine kinase inhibitor-induced corneal ulcers

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A 75-year-old female patient with stage IV adenocarcinoma of the lungs with EGFR exon 21 Leu858Arg mutation presented to the Ophthalmology Department at the Prince of Wales Hospital in Hong Kong in March, 2017, with initial symptoms of bilateral severe dry eyes, followed by sequential ulcerations of the cornea and anterior uveitis causing reduced vision and pain. Blood tests were done and found a substantially raised anti-nuclear antibody titre, positive rheumatoid factor, and syphilis serology (TPPA++ EIA– TP++). Corneal scrapings did not yield any organism growth. The patient denied previous history of syphilis infection but reported a positive drug history of erlotinib use (100 mg daily) for more than 1 year for her lung cancer. Syphilitic uveitis was an unlikely differential diagnosis because examination of her fundi did not reveal any inflammation of the vitreous humour, choroid, or retina, and pupil examination was normal.

Slit-lamp photographs with diffuse and assisted illumination revealed an active roundish ulceration on the right inferonasal cornea with an overlying epithelial defect (figure, A). Her left eye showed a healed ulcer (figure, B). Bilateral curly and elongated lashes, upper lid purplish rashes, and nail dystrophy were observed. A clinical diagnosis of erlotinib-related ophthalmopathy was made.

Her ocular inflammation recurred despite the use of artificial tears, bandage contact lenses, treatment for syphilis (three weekly injections of intramuscular benzylpenicillin [2·4 million units]), and topical and systemic prednisolone. After discussion with her oncologists, her oncologists agreed to discontinue erlotinib and her right corneal ulcer healed within 2 weeks. Later, her oncologists suggested that she switch to gefitinib treatment in view of rising carcinoembryonic antigen levels; however, her corneal ulcer recurred within 1 week after starting gefitinib. Gefitinib was then stopped by the oncologists and the ulcer again healed within 2 weeks. The patient's eyes were stable while on artificial tears, but her carcinoembryonic antigen levels were rising, and the patient refused further chemotherapy as advised by her oncologists.

Ocular side-effects of tyrosine kinase inhibitors are not uncommon, but they usually happen within weeks of initiating treatment. Discontinuing the medication is the most definitive treatment. Severe corneal ulcerations would ultimately lead to perforation and loss of sight. A balance between ocular complications and oncological control should therefore be discussed carefully with the patient. Inter-disciplinary care for such patients is essential.

Contributors
KWK was responsible for study design, literature search, data collection and interpretation, clinical care of the patient, and manuscript writing. PPYW was responsible for literature search, data collection, and manuscript writing. ALY is responsible for data analysis, manuscript writing and review, and supervision. Written informed consent to publication was obtained.

Declaration of interests
We declare no competing interests.

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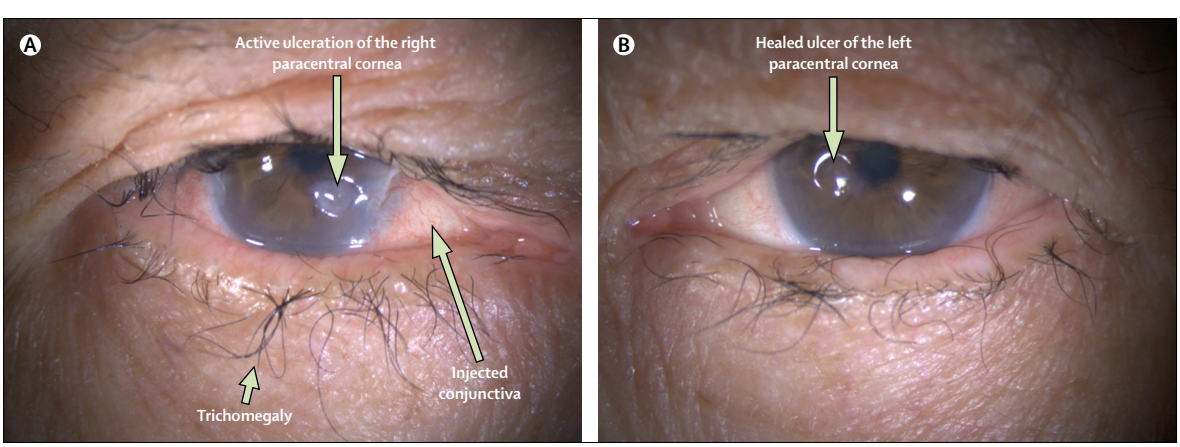

Figure: **Slit-lamp photographs of bilateral corneal ulcers induced by tyrosine kinase inhibitor treatment**
(A) Right eye with conjunctival hyperaemia with active ulceration. (B) Left eye of the same patient reveals a healed ulcer without conjunctival hyperaemia. Trichomegaly is present in both eyes.