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Case Report

Bilateral Severe Corneal Ulcer in a Patient with Lung Adenocarcinoma Treated with Gefitinib

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Keywords
Gefitinib · Neurotrophic corneal ulcer · Non-small cell lung cancer

Abstract
We describe the case of Gefitinib-related bilateral corneal perforation. An 86-year-old female patient had bilateral painless and progressive vision loss due to neurotrophic corneal ulcer, following a 2-month treatment with Gefitinib, a selective epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor for metastatic adenocarcinoma of the lung with confirmed EGFR gene mutation. She had no signs of ocular infection, inflammation, or lid problems to account for the development of corneal damage. Neurotrophic ulcer evolved into a frank perforation in one eye and an impending perforation on the other eye. EGFR inhibitors have been associated with dry eye, epithelial erosions, ulcerative keratitis, and corneal edema. However, to the best of our knowledge, this is the first case of bilateral severe corneal ulcer due to Gefitinib. The patient went on to have bilateral corneal graft surgery. This case aims to raise awareness among ophthalmologists and oncologists of the association between EGFR inhibitors, corneal neurotrophic ulcers, and possible evolution in corneal perforation.

Introduction

Epidermal growth factor receptor inhibitors (EGFR-I) are anticancer agents commonly used in treatment of various solid tumors. Non-Small Cell Lung Cancer (NSCLC) has been associated with abnormalities in the expression of EGFR, thereby requiring targeted therapy

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for these types of patients. In particular, EGFR-I target tyrosine kinase domains preventing the persistent activation of their downstream signaling pathways, and consequent uncontrolled cell proliferation [1].

Lung cancer is a common cause of cancer deaths worldwide. Approximately 85% of patients have a group of histological subtypes collectively known as NSCLC, of which adenocarcinoma and squamous cell carcinoma are the most common subtypes. In 2009, a study established the superiority of Gefitinib over chemotherapy for metastatic NSCLC patients with sensitizing EGFR mutations [2]. Several studies on first (Gefitinib and Erlotinib) and second (Afatinib and Dacomitinib) generation EGFR tyrosine kinase inhibitors (TKIs) showed objective response rate and progression-free survival of patients with sensitizing EGFR mutations, in particular in patients with advanced stages of NSCLC.

The most common side effects of the EGFR-TKIs include rash, diarrhea, anorexia, fatigue, nausea, and vomiting [3]. Ocular side effects develop in about a fifth of patients and include dry eye, trichomegaly, ectropion, keratitis, and persistent epithelial defects [4]. Corneal ulcers and perforations were described with Erlotinib [5] and Afatinib [6]. To our knowledge, there has been only 1 case of unilateral perforating corneal ulceration described with Gefitinib treatment. In this case report, the fellow eye presented no abnormality [7] We present a case of bilateral corneal neurotrophic ulcer, its progression to perforation, and its management in a patient with NSCLC treated with Gefitinib.

Case Report

An 86-year-old female patient had red eyes and painless and progressive vision loss over a 1-month period. The patient had no past history of ocular surface disease or trauma and no features of infection, intraocular inflammation, trichomegaly, ectropion, or entropion. The patient had bilateral wet age-related macular degeneration treated with anti-VEGF injections, the last one 3 years prior.

From a general medical point of view, the patient was affected by metastatic NSCLC and had undergone an upper lobectomy. Molecular investigations showed the presence of an EGFR mutation on biopsy and the patient started treatment with an EGFR-I, called Gefitinib (Iressa®, AstraZeneca Pharmaceuticals, Cambridge, UK), 250 mg/day, for 2 months.

At baseline, she had very low visual acuity, corresponding to counting fingers at 50 cm in the right eye and hand motion in the left eye, with conjunctival hyperemia, deep stromal edema, corneal opacity and, in particular, a bilateral corneal neurotrophic ulcer, worse in left eye (shown in Fig. 1a). We measured corneal sensation using a Cochet-Bonnet esthesiometer (Luneau Ophthalmics, Pont-de-l'Arche, France), and we calculated the mean value of the 5 corneal sectors (central cornea and superior, inferior, temporal, and nasal corneal quadrants). Both eyes presented low corneal sensation, precisely an average value of 17 mm in the right eye and 11 mm in the left eye.

There was no sign of decreased tear breakup time in either eye to suggest dry eye disease, no sign of infection, and no anterior chamber reaction. Therefore, we had decided to apply therapeutic contact lenses and after only 2 days, the eye situation improved, with less inflammatory reaction. An urgent recommendation to discontinue Gefitinib therapy was sent to the treating oncologists, and the drug was stopped.

A few days later, despite bandage contact lenses and slight improvement, the left eye corneal stroma had become very thin as evidenced by anterior segment-optical coherence tomography (shown in Fig. 1b), and we performed a penetrating keratoplasty (shown in Fig. 1c) to avoid a certain corneal perforation trying to obtain a better visual outcome in a

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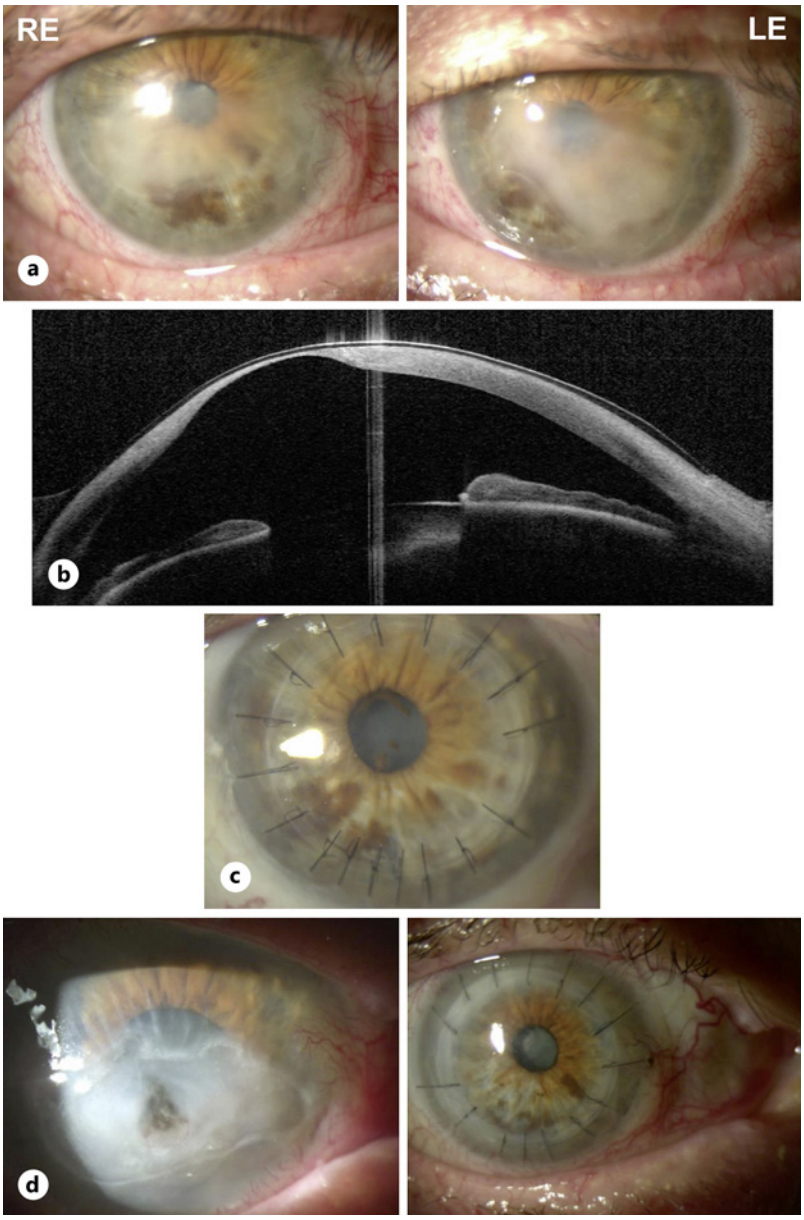

Fig. 1. Case presentation (RE: right eye; LE: left eye) (**a**); the AS-OCT image demonstrates severe stromal thinning in the left eye (**b**); left eye penetrating keratoplasty (**c**); right eye corneal perforation and subsequent penetrating keratoplasty (**d**). AS-OST, anterior segment-optical coherence tomography.

patient with very low visual acuity. Twenty days later, she developed asymptomatic corneal perforation in her right eye and underwent a penetrating keratoplasty in this eye as well (shown in Fig. 1d).

After a short period, the patient's right eye developed an epithelial defect. The epithelial defect improved with the use of a therapeutic contact lens. However, her best-corrected visual acuity, 20/400 in the right eye and 20/800 in the left eye, did not improve much due to a dense cataract and age-related macular degeneration evolved into macular atrophy.

The patient died because of systemic complications. Her husband has given his written informed consent to publish this case (including publication of images).

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Discussion

In this case, the patient was diagnosed with NSCLC with EGFR mutation and she was treated with Gefitinib, a selective EGFR-TKI suppressing tumor cell proliferation. After a 2-month treatment with Gefitinib, she developed a bilateral corneal neurotrophic ulcer and, subsequently, an impending perforation in one eye and a frank perforation on the other eye.

EGFR is expressed in the basal cells of limbal and conjunctival epithelia. EGF, the EGFR ligand, promotes migration and proliferation of epithelial cells, thus facilitating corneal epithelial wound healing. Moreover, endogenous EGF is synthesized by the lacrimal glands in response to corneal epithelial injury. It occurs in high concentrations in tears, and it is important for normal ocular surface homeostasis [8]. The inhibition of the migration and proliferation of conjunctival and limbal epithelial cells can, therefore, explain the pathogenic mechanism underlying EGFR-I ocular toxicity. Studies in rats treated with EGFR-I have demonstrated decreased epithelial thickness, dose-dependent reductions in epithelial wound healing, and decreased epithelial cell division [9].

The use of in vivo confocal microscopy could quantitatively highlight the possible involvement of the sub-basal corneal nerve plexus in EGFR-I toxicity [3]. A significantly lower nerve fiber density caused by EGFR-I can indeed determine persistent epithelial damage, with reduction in corneal thickness and progression toward perforation. Prospective investigations to evaluate in vivo confocal microscopy utility are needed.

The use of EGFR-I is increasing in oncology. Ocular toxicities are generally underestimated and considered minor because priority is given to other life-threatening complications. Ocular disorders are rare, usually transient and mild-moderate, but sometimes irreversible. In our case, the symptoms and signs of corneal toxicity did not improve even though treatment with Gefitinib was stopped. Dose reduction or early drug discontinuance can prevent serious complications in most cases, but the effects on the EGFR could persist further after halting medications [10].

Some authors have speculated about the utility of autologous serum eye drops in counteracting the effects of EGFR-I. Autologous serum eye drops indeed contain many growth factors, including EGF. Nevertheless, there has yet to be an agreement in the use of autologous serum eye drops as being a beneficial action during EGFR-I treatment [5]. Molina-Prat et al. [11] believe that the use of autologous serum eye drops may not be effective with concomitant use of EGFR-I, but instead only effective after EGFR-I discontinuation.

To date, no reports have considered the effectiveness of NGF in ocular surface adverse events of systemic EGFR-I. We think the actual availability of recombinant human NGF eye drops. Cenegermin can improve corneal defects produced by EGFR-I; unfortunately, this ophthalmic drug was not commercially available when we had dealt with this case.

Although ocular toxicities are uncommon, oncologists must recognize ocular toxicity cases and refer those patients with suspect ocular involvement to ophthalmologists. In addition, ophthalmologists have to know the side effects of these drugs on the cornea when they visit theirs patients with corneal neurotrophic ulcers not otherwise explainable (i.e., in absence of known risk factors of the ocular surface), because prompt recognition, early diagnosis, and immediate treatment improve the visual outcome of these patients [12].

Statement of Ethics

This study adhered to the tenets of the World Medical Association Declaration of Helsinki. Written informed consent for publication of case details was obtained from patient's husband, including consent to publish images, because the patient has died.

Conflict of Interest Statement

Marcello Tiseo (M.T.) received speakers' and consultants' fee from AstraZeneca, Pfizer, Eli-Lilly, BMS, Novartis, Roche, MSD, Boehringer Ingelheim, Otsuka, Takeda, and Pierre Fabre. M.T. received institutional research grants from AstraZeneca, Boehringer Ingelheim. The other authors have no conflicts of interest to disclose.

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Author Contributions

The recommendations of the International Committee of Medical Journal Editors were followed for all authors of this article. The authors read and approved the final manuscript. Fabrizio Gozzi made substantial contribution to the design of the work, the acquisition of data, and the drafting of the original work. Marcello Tiseo contributed to the curation of data and revised the work critically for important intellectual content. Francesco Facchinetti made substantial contribution to the curation of data as well as the literature review. Stefano Gandolfi revised the work critically for important intellectual content. Pierangela Rubino made substantial contribution to the conceptualization of the work, the acquisition of data, and the drafting of the original work.

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