

Bilateral Persistent Corneal Epithelial Defect Associated with Erlotinib Treatment

Erlotinib Tedavisi ile İlişkili Bilateral Kornea Epitel Defekti

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ABSTRACT

We report a case of bilateral persisting corneal epithelial defect in a lung cancer patient associated with erlotinib treatment. A 45 years old woman who was treated with erlotinib for lung cancer, presented with bilateral persistent corneal epithelial defect resistant to conservative treatment. Intensive lubrication, moxifloxacin, prednisolone acetate, and bandage contact lens was applied; however, the epithelial defect persisted. After interruption of the erlotinib treatment, the abrasion healed within 2 weeks and had no recurrence. Inhibition of epidermal growth factor receptor (EGFR) may cause a defective corneal epithelial wound repair. EGFR inhibitors such as erlotinib have an increased usage in chemotherapy; therefore ophthalmologists must be aware of their potential ocular side effects.

Key Words: Epidermal growth factor receptor inhibitor, erlotinib, corneal epithelial defect.

ÖZ

Bu çalışmada akciğer kanseri nedeniyle erlotinib tedavisi alan 45 yaşında kadın olguda bilateral persistan kornea epitel defekti gelişimi bildirilmektedir. Terapötik kontakt lens, topikal moksifloksasin, prednizolon asetat ve suni gözyaşı kullanımı ile gerilemeyen bilateral kornea epitel defekti, erlotinib tedavisinin sonlandırılması ile 2 hafta içerisinde kendiliğinden iyileşti ve nüks görülmedi. Epidermal büyüme faktörü reseptörünün inhibisyonu kornea epitelinde iyileşmeyi olumsuz yönde etkileyebilmektedir. Erlotinib gibi epidermal büyüme faktörü reseptörü inhibitörleri kemoterapide gittikçe artan bir kullanım alanına sahip olduğundan, olası yan etkileri açısından oftalmologların dikkatli olmaları gerekmektedir.

Anahtar Kelimeler: Epidermal büyüme faktörü reseptörü, erlotinib, kornea epitel defekti.

INTRODUCTION

Erlotinib (Tarceva; Genentech, Inc, San Francisco, CA) is a selective reversible tyrosine kinase inhibitor of the epidermal growth factor receptor (EGFR) on both normal and tumor cells.^{1,2} Erlotinib was approved by the Food and Drug Administration for the treatment of non-small cell cancer of the lung and pancreas.²

The EGFR is expressed on human corneal, limbal, and conjunctival epithelium and regulates epithelial proliferation, migration, and wound healing.³ Inhibition of the EGFR causes defective epithelial cell proliferation and stratification during corneal epithelial wound repair.⁴ We present a case of bilateral persistent corneal epithelial defect formation due to the use of systemic erlotinib.

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CASE REPORT

A 45 year old woman complained of mild pain and redness in both eyes after 2 months of treatment with erlotinib for a stage 4 lung adenocarcinoma. The patient had no history of ocular medications, irritants, or allergens that may have led to this ocular condition. On examination, her visual acuity was 20/20 in the right eye and 20/60 in the left eye. The slit lamp examination showed corneal epithelial defects in both eyes and severe stromal thinning in the left eye (Figure 1, 2).

There were 2+ cells in the anterior chamber. Corneal culture did not show any organism. The patient was treated with intensive lubrication, topical moxifloxacin, prednisolone acetate, and bandage contact lens. However, her redness, pain and the epithelial defects persisted for 3 weeks.

We suspected that persistent defects may be secondary to the erlotinib treatment. We consulted her oncologist to stop erlotinib treatment because of ocular side effects. After termination of the erlotinib treatment, she was treated with bandage contact lens and artificial tears.

After two weeks her symptoms improved and the corneal epithelial defects disappeared. At her 6 weeks follow-up, there were no recurrences of the defects (Figure 3, 4).

DISCUSSION

The EGFR is a transmembrane protein with an extracellular ligand binding domain and an intracellular protein tyrosine kinase. Activation of EGFR regulates the cell proliferation, apoptosis, and differentiation.⁵ The EGFR inhibition has been used until now for end stage carcinomas refractory or intolerant to chemotherapy.⁶

EGFR inhibitors can be split in 2 groups concerning the site of inhibition and their molecular weights. High molecular weight EGFR inhibitors act in an extracellular binding site (panitumumab), and low molecular weight EGFR inhibitors act in an intracellular binding site (erlotinib).⁷ EGFR is expressed in basal epithelial cells and is believed to be responsible for limbal epithelial mitosis during corneal epithelial cell proliferation.

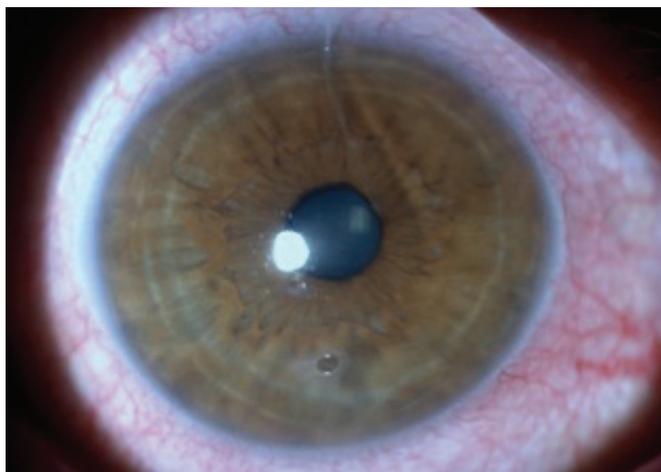


Figure 1: Persistent epithelial defect.



Figure 2: Persistent epithelial defect.

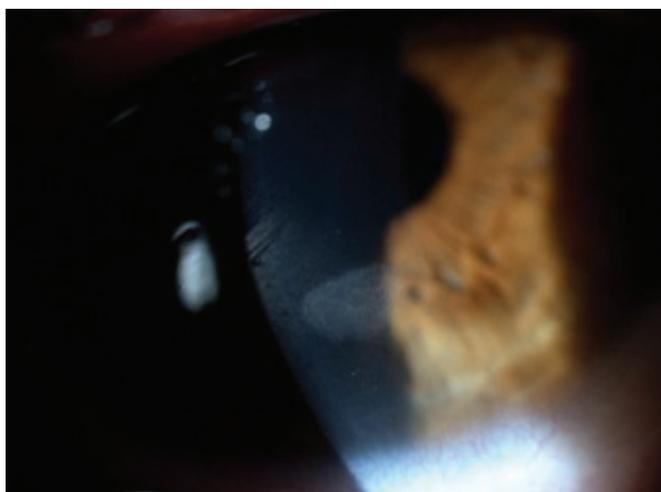


Figure 3: Defect resolved in the right eye after discontinuation of erlotinib.

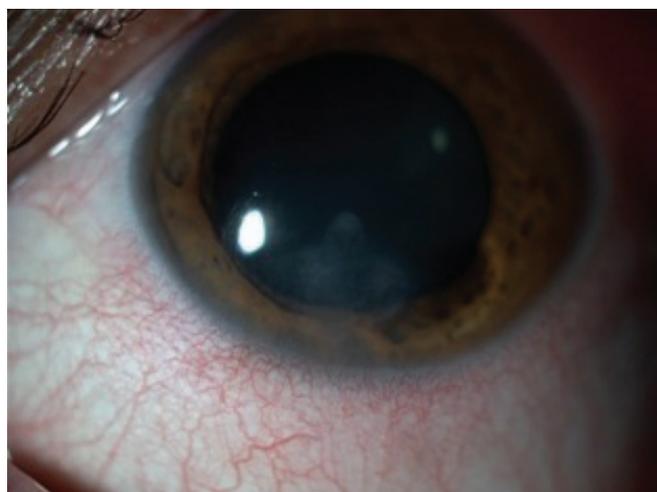


Figure 4: Defect resolved in the left eye after discontinuation of erlotinib.

Corneal wound healing was shown to be significantly delayed after systemic EGFR inhibitor administration in rats.⁴ Cases of trichomegaly and periorbital rash with resultant ectropion have been reported; side effects are believed to be linked to EGFR inhibition.^{8,9} Johnson et al.,¹⁰ described a patient of an infectious keratitis with a persistent epithelial defect undergoing erlotinib treatment, and when EGFR inhibition was discontinued, the erosion healed.

In a previous report, Foerster et al.,¹¹ successfully treated persisting corneal erosion with topical epidermal growth factor which was related to cetuximab. Treatment with EGF or autologous serum may theoretically mitigate the effect of high molecular weight EGFR inhibitors by competing for extracellular EGFR binding sites.

In contrast, low molecular weight inhibitors such as erlotinib act intracellularly at the tyrosine kinase portion of EGFR. Therefore, additional EGF theoretically would not impact the inhibition of enzymatic activity.¹² In this report we describe a case of bilateral persistent corneal erosion in a patient undergoing erlotinib treatment.

Depending on suspension of erlotinib, the erosions regressed within 2 weeks and had no recurrences. In recent years EGFR inhibitors has an increased usage in chemotherapy, therefore ophthalmologists must pay attention to recognize and treat their potential ocular side effects.

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