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Erlotinib induced ectropion following papulopustular rash

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Abstract

Background: Erlotinib is a targeted anti-cancer drug which acts through the inhibition of epidermal growth factor receptor (EGFR).

Main observations: A 79-year-old developed bilateral ectropion after he received erlotinib treatment for lung adenocarcinoma. The ectropion completely resolved with symptomatic treatment without any modification in erlotinib therapy.

Conclusions: EGFR inhibitors are frequently associated with a variety of mucocutaneous adverse events. Ocular toxicity associated with these agents has been reported rarely. We present this case to underline the importance of recognition of newly reported cutaneous and ocular adverse events of targeted therapies. (*J Dermatol Case Rep*. 2015; 9(2): 46-48)

Introduction

Chemotherapeutic agents may be the cause of a wide spectrum of dermatological adverse events affecting the skin, skin appendages and mucous membranes. These adverse events are largely dependent on these agents' mechanism of action in cancer treatment. Recently developed targeted agents in cancer therapy are effective by acting on specific pathways and molecules and are therefore less frequently associated with systemic side effects compared with standard chemotherapy.[1]

Epidermal growth factor receptor (EGFR) inhibitors are increasingly used targeted agents in cancer treatment. EGFR consists of an extracellular ligand binding domain and an intracellular protein tyrosine kinase. Drugs inhibiting the EGFR have different mechanisms of action; while erlotinib, gefitinib and lapatinib inhibit the intracellular tyrosine kinase, monoclonal antibodies like cetuximab and panitumumab bind the extracellular part of the EGFR.[2] FDA approved indications for EGFR inhibitors are lung, breast, pancreatic and colorectal carcinoma.

Basal keratinocytes of the epidermis, hair follicles, sebaceous and eccrine epithelium, corneal, limbal and conjunctival epithelium are among the EGFR expressing cells and tissues.[1-3] The major functions of the EGFR in the skin are regulation of proliferation, differentiation, migration, apoptosis of cells and stimulation of keratinocyte migration and epidermal growth.[1] Therefore, despite their relative safety in terms of systemic toxicity, mucocutaneous side effects are seen rather frequently with EGFR inhibitors.[2]

Case report

A 79-year-old man presented with one-week-history of rash involving his face. He was on his second week of erlotinib treatment for lung adenocarcinoma. His past medical history was insignificant except for hypertension, vertigo and his medications included amlodipine and betahistine. Dermatological examination revealed monomorphic, erythematous papules and pustules over the centrofacial region. Based on the clinical findings, a diagnosis of erlotinib

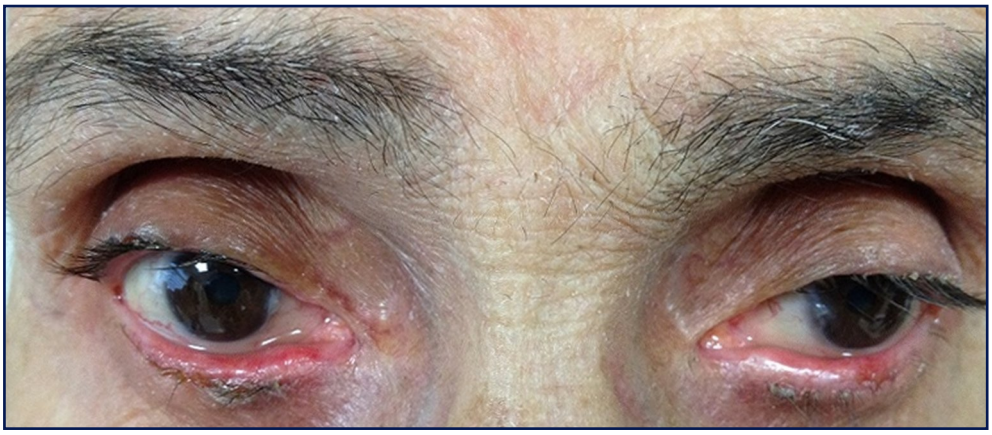

Figure 1
Bilateral ectropion of the lower eyelids.

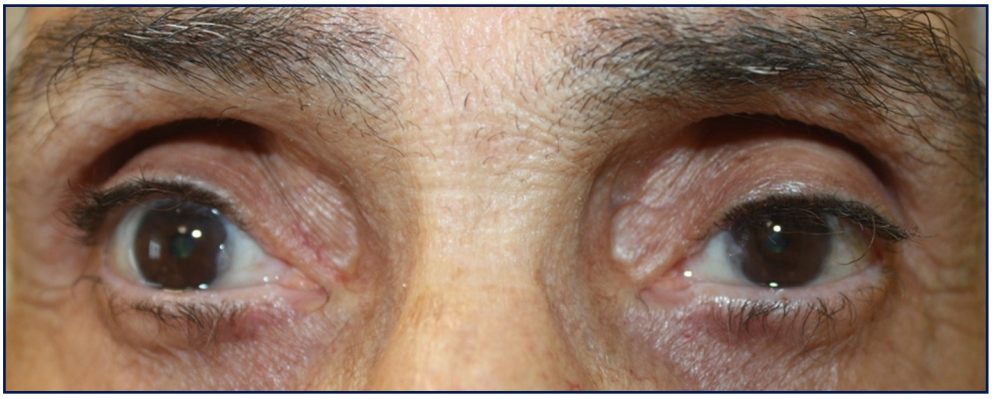

Figure 2
Regression of ectropion and clinically normal appearance of eyelids at 6th month of follow-up.

induced papulopustular rash was made. Treatment with hydrocortisone acetate cream twice daily for three days and sodium sulfacetamide lotion twice daily was commenced. After 3 weeks of treatment, his skin lesions completely resolved but he complained of recently developed burning sensation and dryness in his eyes. Bilateral ectropion of the lower eyelids were noted on physical examination and the patient was referred to ophthalmology department with a presumptive diagnosis of erlotinib induced ectropion (Fig. 1). Ophthalmological examination showed blepharitis, tear film dysfunction leading to dry eye and bilateral ectropion of the lower eyelids. As these findings were mild, no modification in erlotinib treatment was required and the ectropion ameliorated with symptomatic treatment in three weeks. The patient has been followed-up for 6 months and is free of eye related symptoms despite ongoing erlotinib treatment (Fig. 2). Apart from this ocular toxicity, he developed palmoplantar fissures on the fourth month of erlotinib treatment which responded well to topical agents.

Discussion

Erlotinib, as the other EGFR inhibitors, frequently causes mucocutaneous side effects including papulopustular rash, pruritus, xerosis, paronychia, acral fissures, mucositis and hair-nail changes.[2] Ocular toxicity may also occur with erlotinib treatment.[3-6] In a recent review of 69 cases with EGFR inhibitors related ocular toxicity, the most common ocular side effects were dysfunctional tear syndrome, blepharitis, trichomegaly and trichiasis. Other less common toxicities included conjunctivitis, keratitis, corneal ulceration, chalazion and ectropion. The most frequent presenting ocular symptoms were foreign body sensation, dryness and itchiness.[3] These ocular side effects may be associated with inhibition of EGFR which is expressed on corneal, limbal and conjunctival epithelium, however, the exact mechanism still remains elusive. In the previously reported cases of erlotinib-related ectropion, time onset of ectropion ranged between the first and sixth week of erlotinib treatment,[4-6] while it was approximately the fourth week of treatment in the present case. Preceding papulopustular rash associated with erlotinib treatment in our case may have been producing cicatricial traction leading to ectropion development and age related lid laxity may have been contributing to it. However, eye toxicity have also been reported to appear independent of the papulopustular lesions of the face.[3-5]

Ectropion development have been described in association with other anticancer agents as well such as cetuximab and 5-fluorouracil (5-FU).[7,8] In the cetuximab associated case, concomitant use of 5-FU raised the question of cetuximab as the only causative agent of ectropion, however, the authors discussed about the timing of ocular toxicity which, in their opinion, seemed to be unrelated to 5-FU treatment.[7] Cetuximab, also, is an EGFR inhibitor. Ectropion, as many of the other adverse effects, may be regarded as a class effect of EGFR inhibitors, however, the number of reported cases so far is rather small to make a more definite interpretation.

Management decision of erlotinib related ocular toxicities may be given individually depending on the severity of toxicity and the risk-benefit ratio of treatment cessation. Response to anticancer therapy should be the major deciding factor. Despite discontinuation of erlotinib in some cases in literature, ocular toxicities can also be managed conservatively without surgery or treatment modifications as has been done in our case without any drawback.

Conclusions

In the era of targeted therapy in oncology, dermatologists have to keep up-to-date about the newly reported side effects of these drugs. EGFR inhibitor related ectropion, due to its likely association with skin toxicity, may first be noticed by dermatologists. Familiarity with the spectrum and course of side effects of targeted agents is also important for ophtalmologists as ocular toxicities seem not to be so uncommon. A collaboration between managing physicians is mandatory to give the most appropriate decision paying a special attention on response of cancer to treatment.

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