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Erlotinib-induced Rosacea-like Dermatitis

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ABSTRACT Skin and skin adnexa toxicities are the most common side effects associated with epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) and occur in most patients receiving this therapy. The majority of these cutaneous side effects are transient, reversible, and dose dependent. Although these symptoms are in general not severe, they significantly affect quality of life and can have a serious effect on treatment compliance as well as the treatment regimen. The most common early symptoms present as papulopustules on an erythematous base, usually localized in seborrheic areas. This clinical presentation is commonly described as "acneiform", although these adverse reactions have clinical presentations, such as rosacea-like and seborrheic-like dermatitis. In this context, we report a case of a 77-year-old man with a medical history of planocellular lung cancer with ipsilateral pulmonary metastasis and mediastinum infiltration who received erlotinib as a third-line therapy, presenting with centrofacial rosaceiform rash as a side effect associated with the use of EGFR-TKIs. The patient had a negative previous history of rosacea. Therefore, symptoms probably occurred as an adverse reaction due to the oncological therapy. Current terminology of early cutaneous adverse reactions caused by EGFR-TKIs refers to "acneiform" or "papulopustular" lesions, excluding less common side effects such as rosacea-like dermatitis so these symptoms might be overlooked and misdiagnosed. Thus, we would like to emphasize the importance of developing a more accurate classification of terms in order to provide early detection of all possible cutaneous side effects, including less common ones, providing specific and timely treatment, and allowing continuation of drug therapy.

KEY WORDS: skin toxicities, EGFR tyrosine kinase inhibitor, rosacea-like dermatitis, erlotinib

INTRODUCTION

Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) are among the most extensively used targeted agents for the treatment of advanced metastatic tumors such as non-small cell lung cancer (NSCLC), breast cancer, and pancreatic cancer. The Food and Drug Administration (FDA) has

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approved erlotinib, a small-molecule EGFR-TKI, for the treatment of NSCLC and pancreatic cancer. As a result of its high specificity it is characterized by low systemic toxicities. Although targeted therapies avoid common cytotoxic chemotherapy side effects, their use is associated with high frequency of cutaneous toxicities. The most common cutaneous side effects of erlotinib, as well as other epidermal growth factor receptor inhibitors (EGFRIs), are skin lesions that are commonly classified as "acneiform" or "papulopustular rash".

In order to draw attention to other rare clinical presentations of these cutaneous adverse reactions as well as to discuss the accuracy of their present classification, we report the case of a male patient who developed rosacea-like dermatitis after erlotinib initiation.

CASE REPORT

A 77-year-old man was referred to our Department with a current medical history of planocellular lung cancer with ipsilateral pulmonary metastasis and mediastinum infiltration. Erlotinib, as a third-line therapy, was initiated 17 days prior to our examination. Seven days after the initiation of erlotinib, the patient developed centrofacial rosaceiform rash. The patient's medical history was negative for rosacea as well as rhinophyma. Prior to the initiation of erlotinib, he had received four cycles of gemcitabine and cisplatin as a first-line chemotherapy for advanced NSCLC, and two cycles of docetaxel as a treatment for locally advanced or metastatic NSCLC after the failure of prior platinum-based chemotherapy. The patient presented with disseminated erythematous, papular, and dried out pustular lesions, scales, and crusts localized in the centrofacial area (Figure 1) with an intensive sensation of itching and sensitive skin. There were no lesions on the thorax. Additionally, the patient presented with fluorescein positive corneal epithelial erosion, which regressed after topical antibiotic treatment. The patient's general condition was good, although he had suffered from chronic renal insufficiency and partial respiratory insufficiency. Considering the clinical symptoms that were highly suggestive of rosaceiform dermatitis, and recent reports suggesting EGFR-TKIs may aggravate rosacea or induce rosacea-like symptoms, a biopsy was not planned. The patient tested negative for *Demodex fol-*

Table 1. Specific skin score for acneiform eruptions induced by epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs)

A = Body involvement – **0**	
B = Facial involvement (extent of lesions on the face, 0-100%) – **40%**	
C = Skin lesion score (sum of erythema intensity, erythema distribution, papulation, pustulation, and scaling/crusts, 0-3 each):	
erythema intensity	**1.5**
erythema distribution	**1.5**
papulation	**1**
pustulation	**1**
scaling/crusts	**2**
total:	**7**
Final score	
1/4A + 1/4B + 10/3C = 0 + 40/4 + 7x10/3 = 0 + 10+ 23.3 = 33.3	

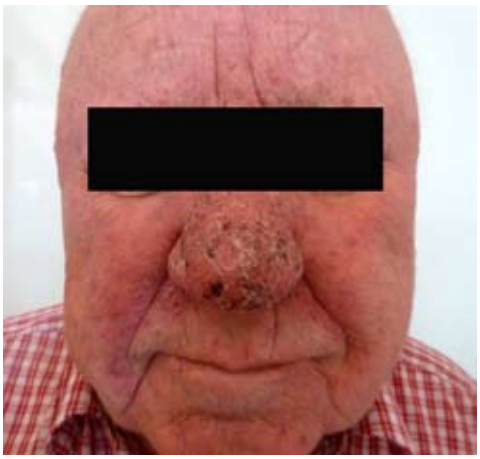

Figure 1. Centrofacial rosaceiform rash with disseminated erythematous papular and dried out pustular lesions, scales, and crusts.

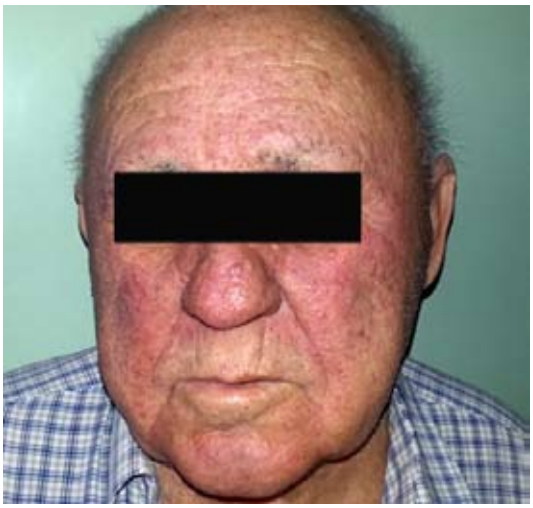

Figure 2. Significant regression of centrofacial erythema and papular lesions after use of a fixed combination of topical corticosteroids and antibiotics (betamethasone, gentamicin) as well as cold compresses twice daily for ten days.

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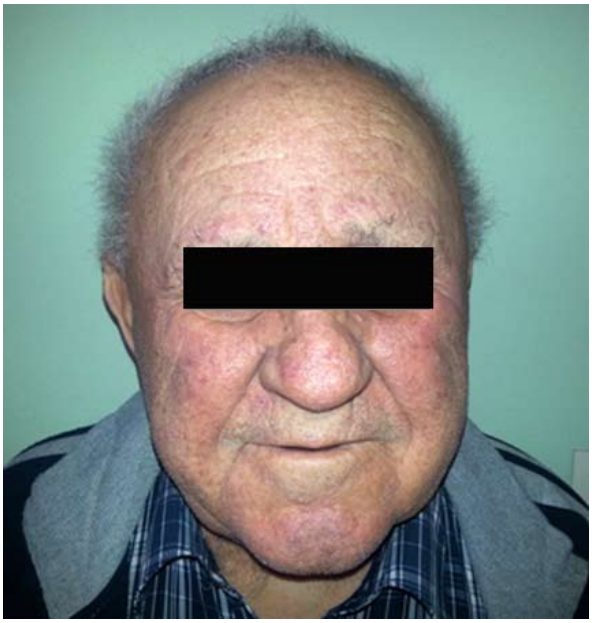

Figure 3. Complete regression of skin lesions after discontinuation of erlotinib.

liculorum. A quantification of the adverse reaction of all body regions with the specific skin score for acneiform eruptions induced by EGFR-TKIs was performed (1). The final score was 33.3, indicating moderate acneiform eruption (Table 1) (1). Following recent guidelines on treatment strategies for EGFR-TKIs side effects, a fixed combination of topical corticosteroids and antibiotics (betamethasone, gentamicin) as well as cold compresses were administered twice daily for ten days (2-5). On post-therapeutic follow-up examination two weeks later, the papular lesions and centrofacial erythema had been significantly diminished, as well as the patient's symptoms of itching and sensitivity (Figure 2). He was prescribed local metronidazole and advised to avoid sun exposure, as well as to continue use of cold compresses. Two months afterwards the patient completed the scheduled EGFR-TKIs therapy and came to our Department for a final examination, which showed complete regression of all skin lesions (Figure 3). As a result of the quick and satisfactory therapeutic effect of the prescribed local therapy, there was no need for dose adjustment or discontinuation of erlotinib therapy.

DISCUSSION

EGFR-TKIs avoid chemotherapy-related adverse effects but are commonly associated with adverse skin reactions, which are frequently observed in up to 80%-90% of patients receiving targeted treatment (4-8). Cutaneous complications of these medications develop as a result of the alteration in epidermal differentiation and proliferation and hair growth, due to the inhibition of the epidermal growth factor receptor (EGFR), which is expressed in epidermal cells, sebaceous glands, and hair follicles (5,6). EGFR is also expressed in the basal epithelial cells across the cornea and limbal basal cells where it is considered important for corneal epithelial cell proliferation and wound healing (9). Erlotinib is an oral, highly selective tyrosine kinase inhibitor that targets EGFR to inhibit tumor cell growth and proliferation (4). It has been approved by the FDA for the treatment of NSCLC and pancreatic cancer in combination with gemcitabine (4). Clinical trials on erlotinib have demonstrated it can lead to a variety of skin toxicities that are classified as early and late cutaneous adverse reactions (4-7,10,11). Although the pathophysiological mechanism for the development of these skin disorders is not yet fully understood, there is more evidence of cutaneous infectious complications in patients using EGFR inhibitors, probably due to impairment of the epidermal barrier and antimicrobial defense mechanisms that enable the secondary infection to occur (2,12,13). Acneiform rash, characterized by papulopustules and usually presenting in seborrheic areas, is the earliest common side effect of EGFR-TKIs, appearing on the 2nd and 3rd week of the treatment in 45-100% of cases (7,10,11). Although the rash is often termed "acneiform" or "papulopustular", these skin lesions are pathologically and clinically different from acne vulgaris due to the absence of comedones, the presence of subjective symptoms of itching and sensitive skin, and satisfactory response to topical treatment with metronidazole and high potency topical corticosteroids (5,8,14). Furthermore, cases of folliculitis and *Malassezia sympodialis* have also been reported as early skin side effects, as well as cases of diffuse erythema and telangiectasia (5,13,15-17). Due to recent data showing increased density of *Demodex folliculorum* in the skin of the patients receiving EGFRIs, some researchers have also suggested introducing a new term, "rosacea-like" or "rosaceiform" dermatitis (14). Since grading and classification of these skin lesions have mostly been done by oncologists, the term "acneiform rash" or "papulopustular rash" covers a broad spectrum of different clinical presentations including pustular, papular, pruritic, erythematous, or generalized rash, acneiform exfoliative dermatitis, and dry skin (8,12). Due to these different clinical presentations that can mimic other dermatological conditions and the current classification that has not proven to be accurate enough, differential diagnosis can be truly challenging (5). Due to the importance and necessity of accurate grading of early EGFR inhibitor cutaneous adverse events, several grading scales

have had been developed, including the National Cancer Institute's Common Terminology Criteria for Adverse Events version 4.0 (NCI-CTCAE v4.0) as the most widely used one, and the Multinational Association of Supportive Care in Cancer (MASCC) Skin Toxicity Study Group which was developed specifically for these targeted agents, resulting in improved sensitivity and specificity (2,5-7,11). Nevertheless, these grading scales also have limitations and deficiencies because they imply "acneiform" or "papulopustular" rash is the only clinical presentation of these early cutaneous adverse reactions. Furthermore, there are also late cutaneous adverse reactions usually developing several weeks after the initiation of EGFR tyrosine kinase inhibitor treatment including xerosis, skin fissures, alterations in hair growth, hyperpigmentation, and telangiectasia (5,6,8,11,18). Nail disorders including paronychia, periungual abscesses, and pyogenic granuloma may also develop (5,8). Although the clinical presentation of cutaneous adverse reactions of EGFR-TKIs is moderate in the majority of cases, if left untreated it can affect the patient's quality of life (QoL), leading to stigmatization and a large psychological burden as well as interfering with treatment compliance, leading to drug reduction or discontinuation of the treatment (4-7,18). We report this case in order to draw attention to rosacea-like dermatitis as a possible cutaneous adverse reaction of EGFR-TKIs, emphasizing the need for more accurate classification of these side effects that are presently classified as "acneiform" or "papulopustular" lesions, despite the fact that the side effect can have a number of quite different clinical patterns.

CONCLUSION

The term "acneiform rash" or "papulopustular rash" does not sufficiently illustrate other clinical forms that are not as common, but are nevertheless also associated with EGFR-TKIs. The great heterogeneity in the definitions of these skin toxicities must be acknowledged, as they are reported differently in research and trials. Accordingly, their accurate classification is of crucial importance in order to provide early detection and timely treatment, enabling continuation of EGFR –TKI treatment without any alterations.

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