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ORIGINAL RESEARCH

Scalp Pustule as a Manifestation of Erlotinib-Induced Skin Toxicity: Report of Two Cases and Literature Review

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Introduction: Erosive pustular dermatosis of the scalp (EPDS) is a rare, chronic inflammatory disorder characterized by sterile pustules, erosions, crusting, and scarring alopecia, which has been occasionally reported in association with epidermal growth factor receptor inhibitors (EGFRIs).

Methods: We report two cases of EPDS induced by erlotinib therapy for non-small cell lung cancer (NSCLC). Case 1 involved a 73-year-old female with four years of erlotinib use presenting with scalp pustules, alopecia, and scarring. Case 2 was a 37-year-old male who developed papulopustular lesions on the scalp and trunk after six months of erlotinib therapy. Histopathological examination was performed on biopsy samples from both EPDS patients and compared with samples from two healthy controls.

Results: Comparative analysis revealed neutrophilic infiltration, irregular epidermal hyperplasia, and elevated EGFR expression in hair follicles and epidermal keratinocytes in EPDS patients versus controls. These findings demonstrate how EGFR inhibition disrupts keratinocyte function and triggers inflammatory responses leading to severe follicular damage.

Conclusion: These cases highlight the importance of dermatological monitoring in patients undergoing EGFRI therapy. Early recognition and management with antibiotics and topical steroids may help mitigate adverse effects. Further research is needed to elucidate underlying mechanisms and optimize treatment strategies for EPDS.

Keywords: erosive pustular dermatosis of the scalp, EPDS, epidermal growth factor receptor inhibitors, EGFRIs, erlotinib, neutrophilic inflammation, cutaneous adverse reactions, alopecia

Introduction

Epidermal growth factor receptor inhibitors (EGFRIs), such as erlotinib and gefitinib, are widely used in the treatment of non-small cell lung cancer (NSCLC) and other malignancies. Cutaneous toxicities associated with these agents are well documented and range from acneiform eruptions and xerosis to pruritus and, more rarely, erosive pustular dermatosis of the scalp (EPDS). EPDS is a rare, chronic inflammatory dermatosis characterized by sterile pustules, erosions, crusting, and scarring alopecia. Although its pathogenesis remains incompletely understood, dermal neutrophilic infiltration and follicular damage are frequently observed.[1,2] In this study, we report two cases of erlotinib-induced EPDS and review the histopathological features of this rare skin toxicity, summarizing the clinical manifestations and pathological findings in comparison with other reported cases of EGFR inhibitor-induced EPDS. These findings add to the growing evidence that EGFR inhibition may contribute to neutrophil-mediated cutaneous inflammation beyond typical acneiform presentations.

Materials and Methods

In this study, tissue samples from two patients diagnosed with EPDS and two healthy controls were collected and analyzed. The healthy control group consisted of two males aged 38 and 41 years. This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and was approved by the Ethics Review

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Committees (ERC) of the Dermatology Hospital of Southern Medical University, Guangzhou, China. Written informed consent was obtained from all participants prior to sample collection.

To evaluate EGFR expression, immunohistochemistry (IHC) was performed using a specific anti-EGFR antibody. The IHC staining results were independently assessed by two experienced pathologists to ensure accuracy and consistency. Additionally, pathological analysis was conducted to further characterize the tissue samples and compare the differences between EPDS patients and healthy controls.

Case Presentation

Case 1

A 73-year-old female was admitted to the hospital due to recurrent scalp pustules, alopecia, desquamation, and scarring for five months. She had been using erlotinib for four years and had a medical history of diabetes and lung cancer. The physical examination revealed the presence of diffuse alopecia on the vertex, generalized erosion and crusting with subsequent scar formation at the base, and dense or scattered pustules. When bacterial and fungal cultures of secretions from the skin lesions were analyzed in the lab, no notable anomalies were found. However, the histopathological examination of the skin lesions detected abscess formation, irregular epidermal hyperplasia, cavernous transformation, infiltration of inflammatory cells into the epidermis, superficial dermal hyperedema, vasodilation, and a significant number of neutrophils, lymphocytes, and plasma cells infiltrating around the hair follicle (Figure 1).

Case 2

A 37-year-old male patient who presented with papulopustular lesions accompanied by pruritus on the scalp, face, trunk, and extremities for six months. Six months prior, the treatment of non-small cell lung cancer began with oral erlotinib (150 mg q.d). The physical examination revealed densely distributed erythematous papules, pustules, and erythematous nodules on the scalp, some of which merged to form plaques with associated alopecia. The hair pull test yielded a positive result. The skin of the face, chest, shoulders, and limbs showed sporadic red papules with a few pustules and hyperpigmentation on the lower limbs. No significant abnormalities were found in the laboratory analyses of bacterial and fungal cultures of secretions obtained from skin lesions. The pathological examination of the scalp tissue showed increased hair follicles in the telogen phase, a higher density of plasma cells surrounding the follicles, and lymphocytic infiltration. Pathological examination of the longitudinal segment of scalp tissue revealed the presence of many neutrophils, tiny neutrophilic abscesses, partially elongated skin processes, and parametratosis of the epidermis (Figure 2). Positive expression of the EGFR was seen in the basal layer of both hair follicles and the epidermis (Figure 3). The histopathological assessment of the left thigh revealed subepidermal pustules with

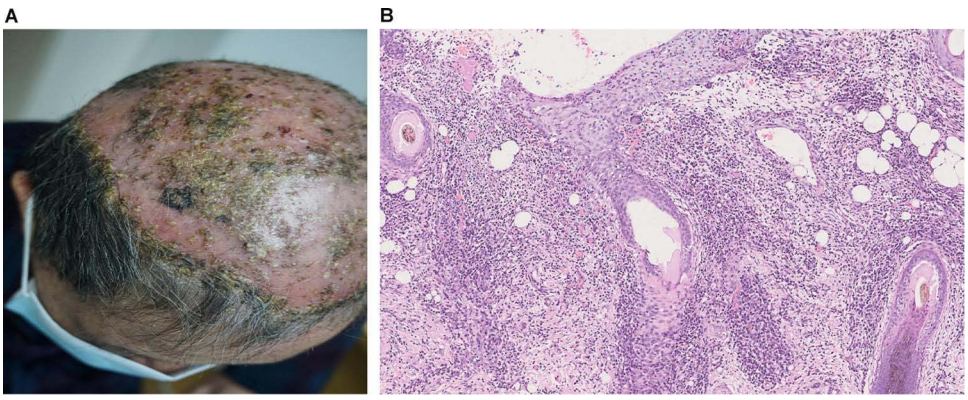

Figure 1 Cytological, histological, and morphological manifestations in Case 1. (**A**) Physical examination revealed the presence of diffuse alopecia on the vertex, generalized erosion and crusting with subsequent scar formation at the base, and dense or scattered pustules. (**B**) Histopathological examination of the skin lesions detected abscess formation, irregular epidermal hyperplasia, cavernous transformation, infiltration of inflammatory cells into the epidermis, superficial dermal hyperedema, vasodilation, and diffused neutrophils, lymphocytes, and plasma cells infiltrating around the hair follicle (200×).

significant infiltration of neutrophils in both the pustular and epidermal regions. Superficial dermis edema along with erythrocytes extravasation a limited number of lymphocytes surrounding the blood vessels, and neutrophils within the blood vessels (Figure 4).

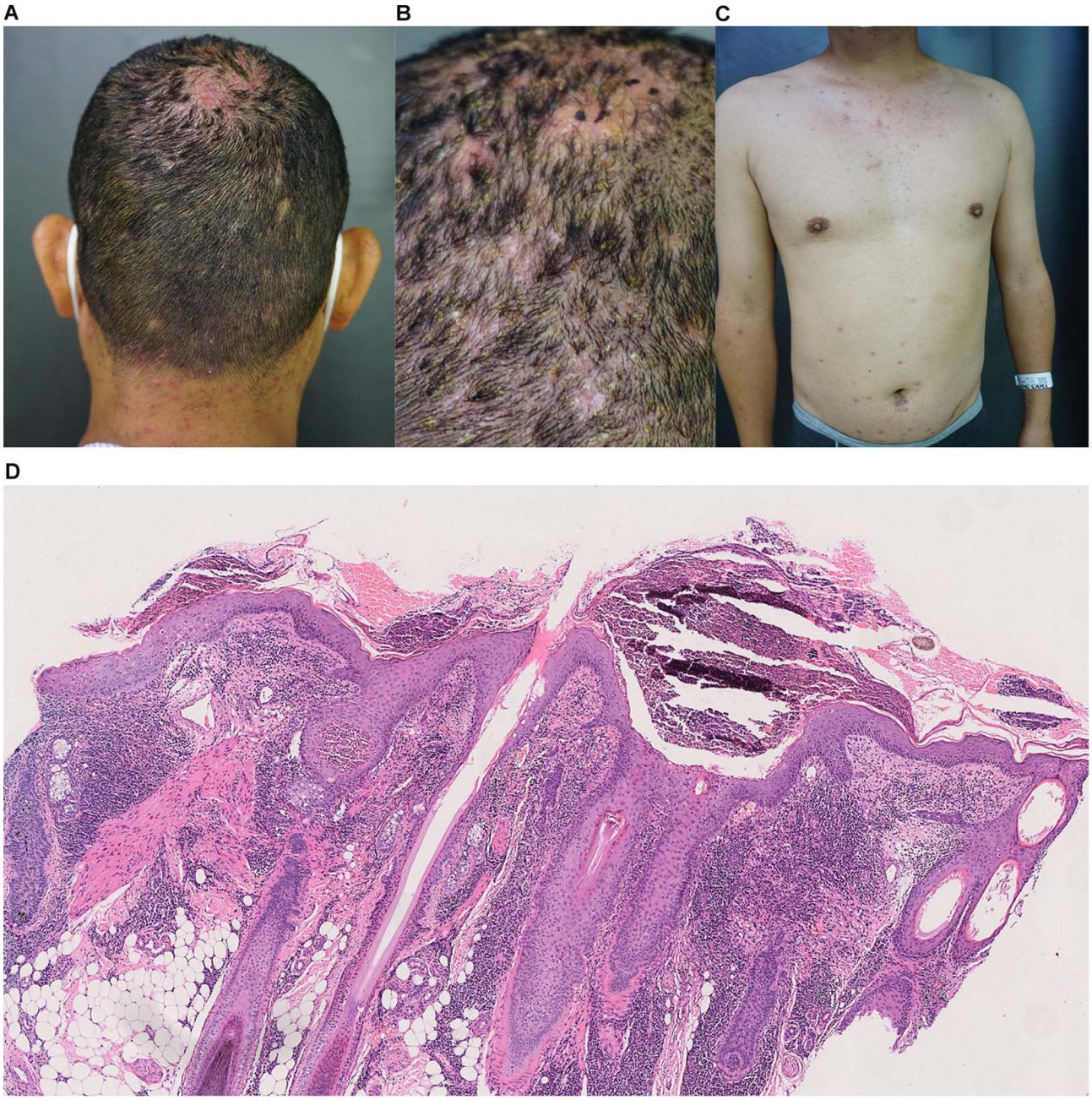

Figure 2 Cytological, histological, and morphological manifestations in Case 2. (**A-C**) Physical examination revealed densely distributed erythematous papules, pustules, and erythematous nodules on the scalp, some of which merged to form plaques with associated alopecia. Skin of the face, chest, shoulders, and limbs showed sporadic red papules with a few pustules and hyperpigmentation on the lower limbs. (**D**) Pathological examination of the scalp tissue showed increased hair follicles in the telogen phase, a higher density of plasma cells surrounding the follicles, and lymphocytic infiltration. Pathological examination of the longitudinal segment of scalp tissue revealed irregular acanthosis, the presence of many neutrophils, tiny neutrophilic abscesses and parametratosis of the epidermis (40×).

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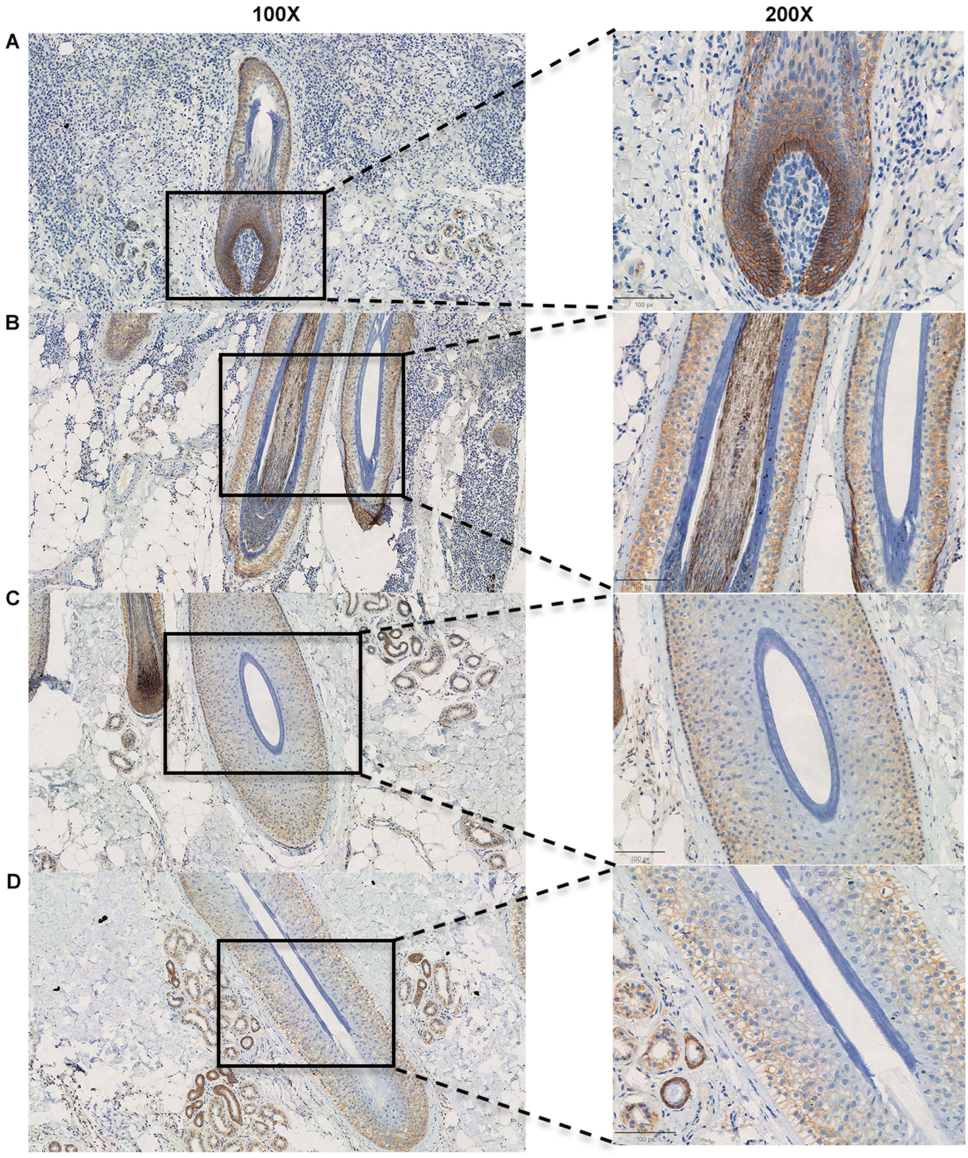

Figure 3 EGFR expression in scalp hair follicles of Case 1, Case 2, and healthy controls. (**A** and **B**) IHC staining of EGFR in the scalp hair follicles of Case 1 and Case 2, respectively. (**C** and **D**) Represent the two healthy control groups. EGFR expression was significantly higher in the undifferentiated keratinocytes of both the outer layer of the hair follicles and the basal layer of the epidermis in the patients (**A** and **B**) compared to the healthy controls (**C** and **D**). Higher magnification images (right panels) highlight the distribution of EGFR-positive cells in these regions. Scale bars: 1355 μm (100×, left panels) and 677.5 μm (200×, right panels).

Discussion

Epidermal growth factor receptor inhibitors (EGFRIs) represent a class of targeted chemotherapeutic agents predominantly employed in the management of malignant neoplasms, including non-small cell lung cancer (NSCLC) and colorectal cancer (CRC). EGFR is a transmembrane glycoprotein consisting of an extracellular domain that binds to ligands and an intracellular tyrosine kinase domain. Once activated, EGFR initiates a cascade of downstream signaling pathways that promote cellular proliferation, migration, angiogenesis, and inhibition of apoptosis, thereby facilitating tumorigenesis and cancer progression. Currently, the most commonly utilized EGFRI encompass the first-generation agents such as gefitinib, erlotinib, and icotinib; the second-generation inhibitor afatinib; and third-generation agent osimertinib. EGFR is expressed not only in cancer cells but also in the undifferentiated hyperplastic keratinocytes located in the basal layer of the epidermis and the outer layer of the hair follicles. The pharmacological inhibition of EGFR in these non-malignant cells can lead to a spectrum of cutaneous adverse effects. The underlying mechanisms involve two primary pathways: (1) the disruption of keratinocyte growth, proliferation, migration, and differentiation; and (2) the

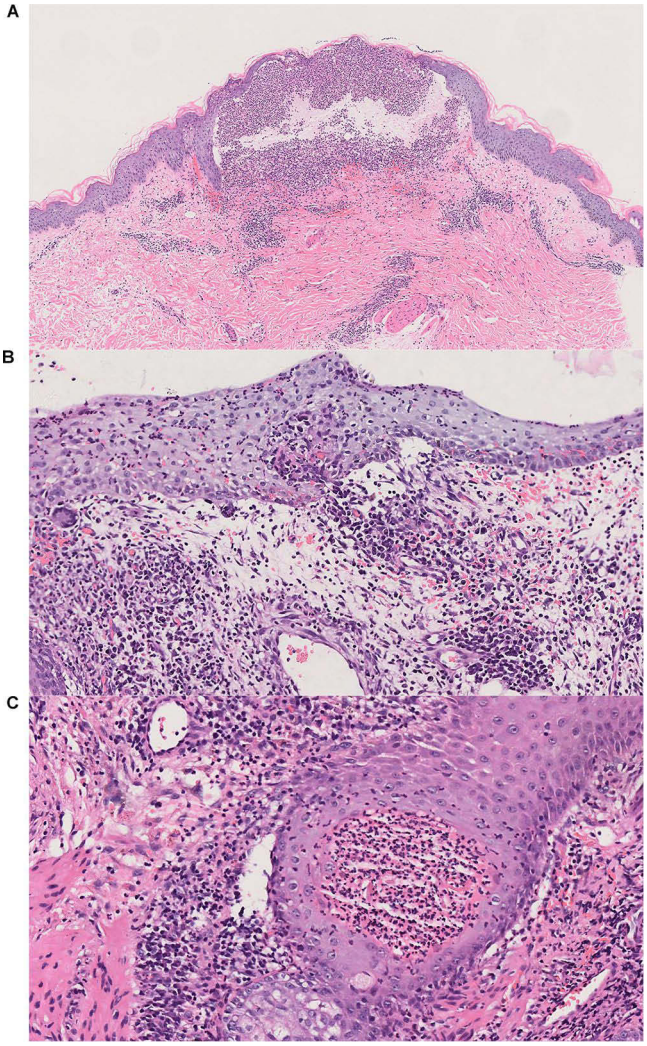

Figure 4 Cytological and histological manifestations in Case 2. (**B**) Histopathological examination of the skin lesions detected irregular epidermal hyperplasia, cavernous transformation, infiltration of inflammatory cells into the epidermis, superficial dermal hyperedema, vasodilation. (**A** and **C**) Histopathological assessment of the left thigh revealed subepidermal pustules with significant infiltration of neutrophils in both the pustular and epidermal regions. Edema was observed in the superficial dermis, along with extravasation of erythrocytes, a limited number of lymphocytes surrounding the blood vessels, and neutrophils within the blood vessels in Case 2. Scale bars = 50 μm in (**B**) and (**C**) and 250 μm in (**B**) (a: 40×; b: 200×; c:200×).

modulation of cytokine and chemokine profiles, which induces inflammatory infiltration and immune cell recruitment, ultimately compromising the integrity of epidermal tight junctions and the cutaneous barrier function. Therefore, the inhibition of EGFR functions can cause a range of dermatological manifestations, including but not limited to acneiform rash, pruritus, xerosis, hyperpigmentation, erosive pustular dermatosis of the scalp (EPDS), and alopecia. Among these, the acneiform rash is the most frequently observed adverse event and is considered a potential pharmacodynamic biomarker indicative of treatment efficacy.[1] This cutaneous toxicity profile underscores the importance of dermatological monitoring and management in patients undergoing EGFRI therapy.

Neutrophils have been linked to cutaneous adverse responses generated by EGFRI, according to recent theories. Lubbe et al first reported a case of generalized dermatosis characterized by neutrophilic spongiosis following oral administration of erlotinib. An additional manifestation of neutrophilic inflammation induced by EGFRI was suspected in this case.[2] Then, Lakshmi et al documented the first instance of lapatinib-induced acute generalized expulsive pustulosis (AGEP). AGEP is a pustular rash primarily induced by medications, frequently accompanied by fever and increased neutrophil count.[3] Further, Bellini et al examined the pathological sections of 39 patients who developed an erythematous papulopustular rash after EGFRI treatment (primarily with cetuximab and erlotinib). Early symptoms were pleomorphic

infiltration in the superficial dermis and intraepidermal neutrophilic pustules; later symptoms included suppurative folliculitis and/or lymphocytic perifolliculitis.[4] Billi et al discovered that the combination of EGFR/MEK inhibitors and *C. dermatometaica* induced IL-36γ release in keratinocytes, which subsequently contributes to the inflammatory response and neutrophil recruitment. This mechanism helps explain the typical pustular and follicle-centered rash caused by these inhibitors. The findings highlight how *C. dermatometaica* plays a key role in triggering the inflammatory cascade, bolstering the practical application of antibiotics in managing these side effects.[5]

Compared to the cutaneous toxicities linked to EGFRI, the incidence rate of EPDS is quite modest. This disorder is a form of primary cicatricial alopecia that typically manifests on the scalp and is more prevalent among elderly female patients. The condition is characterized by persistent inflammation, erosion, crusting, and scarring. In recent years, reclassifying the disease as neutrophilic dermatosis has been suggested. Cases of EPDS induced by EGFRI, gefitinib, and PD-1 have been documented; however, erlotinib, an EGFRI drug, has been infrequently associated with EPDS. Toda et al reviewed the reports of 11 cases of alopecia linked to EGFRI and summarized the findings; all patients in these cases were older women. Three years or less passed between the start of the medication and the development of scalp lesions for the medications that were implicated: lapatinib, erlotinib, and gefitinib.[6] Early non-infectious erythematous alopecia eventually progressed to cicatricial alopecia.

Nevertheless, it is yet unknown how EGFRI causes EPDS. EPDS caused by gefitinib may be linked to the autoinflammatory reaction brought on by damage to the outer sheath of the hair root caused by EGFRI. EGFR is expressed in the outer root sheath of the hair and is involved in regulating cell cycle progression from phase G1 to phase S; thus, the blockade of EGFR-mediated signaling leads to a transition from the growth phase. The inhibition of EGFR is also linked to ultraviolet-induced apoptosis of keratinocytes, barrier impairment (elevated levels of keratinization markers and disruption of intercellular junctions), skin atrophy, as well as local trauma such as that caused by radiation therapy or actinic damage. Scalp tissues of the two patients with EPDS in our cases and two healthy controls were examined (Figure 3). The undifferentiated keratinocytes found in the outer layer of the hair follicles and the basal layer of the epidermis were found to have abundant expression of EGFRs, suggesting that the drug's target tissues are the hair follicles and the scalp. Consequently, the erosion of the scalp and eruption of follicular-papular lesions represent prominent clinical manifestations associated with this drug-induced reaction. Moreover, the expression of EGFR was found to be higher around the hair follicles in the two patients compared to the healthy controls. The increase in EGFR expression may lead to a greater impact of the medication on patients, which may account for the severe hair follicle damage and more pronounced clinical symptoms observed in these two cases compared to typical patients. Although our study is limited by the number of cases, our data provides some evidence on the role of EGFRI in the pathogenesis of such severe follicular inflammation. Further large-scale detailed investigation is required for elucidation of the underlying mechanisms and pathways.

The participation of neutrophils as a critical mediator of inflammation sets apart neutrophil-mediated drug rash.[7] Beech et al proposed that the cutaneous toxic effects of EGFRI exhibit temporal variation, with patients who experience toxicity after six months of treatment presenting distinct symptoms from those who developed toxicity within two weeks.[8] Whether it is an early acneiform rash, a later stage of EPDS, or AGEP (as mentioned above), these cutaneous toxic reactions are characterized by prominent neutrophilic infiltration in their pathology, which partially overlaps with the findings of neutrophilic dermatosis. In the two patients reported here, pustules were observed as initial symptoms, accompanied by evident pathological infiltration of neutrophils, indicating disease homogeneity. While EPDS may show up as a late-stage change, the acneiform rash is frequently seen and happens early in the course of the disease, even if the clinical presentations of EGFRI vary.

Patients with acneiform eruptions respond somewhat to the treatment that is currently being used. The majority of such patients have shown significant improvement following isotretinoin administration, with insignificant adverse reactions. Beshay et al established satisfactory therapeutic effects of dapsone administration implemented for the treatment of severe acneiform rashes unresponsive to oral tretinoin, minocycline, and doxycycline.[9] Previous case reports have shown that EPDS caused by EGFRI had a poor response to hormonal therapy.[10] Furthermore, EGFRI skin toxicity can negatively impact patients' medication adherence, and high doses of therapeutic drugs may lead to adverse effects. The prophylactic administration of oral antibiotics and topical steroids has been shown to significantly decrease the occurrence of skin toxicity. Therefore, prompt treatment with oral tetracycline and topical steroids upon symptom onset is recommended as first-line therapy. Isotretinoin, on the other hand, is typically reserved for more severe or refractory cases.

Conclusion

This study highlights two cases of erlotinib-induced cutaneous toxicity, manifesting as scalp pustules and EPDS, characterized by neutrophilic infiltration and elevated EGFR expression in hair follicles and epidermal keratinocytes. The findings suggest that EGFR inhibition disrupts keratinocyte function and triggers inflammatory responses, leading to severe follicular damage and clinical symptoms. The study underscores the importance of early recognition and management of EGFRI-related skin toxicities, including the use of antibiotics and topical steroids, to improve patient outcomes. Further research is needed to elucidate the underlying mechanisms and optimize therapeutic strategies for these adverse effects.

Ethics Statement

This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. The publication of case details and accompanying images was approved by the Ethics Review Committee (ERC) of the Dermatology Hospital, Southern Medical University, Guangzhou, China. Written informed consent was obtained from all participants, including both patients and healthy controls, for participation in the study and for publication of their anonymized case details and clinical images. All identifying information has been removed to protect patient confidentiality.

Author Contributions

All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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