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CASE REPORT

A Case of Cicatricial Alopecia Associated with Erlotinib

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Erlotinib is a small-molecule tyrosine kinase inhibitor (TKI) of the epidermal growth factor receptor (EGFR). Erlotinib has been used primarily to treat non-small cell lung cancer. In addition to its role in tumor cells, EGFR is also an important regulator of growth and differentiation in the skin and hair. Therefore, EGFR-TKIs have been associated with a number of cutaneous side effects including follicular acneiform eruptions, cutaneous xerosis, chronic paronychia, desquamation, seborrheic dermatitis, and hair texture changes. Herein, we report a rare case of a 61-year-old woman who was treated with erlotinib and experienced cicatricial alopecia. **(Ann Dermatol 23(S3) S350～S353, 2011)**

-Keywords-
Cicatricial alopecia, Epidermal growth factor receptor, Erlotinib

INTRODUCTION

Erlotinib is a tyrosine kinase inhibitor (TKI) that selectively inhibits the epidermal growth factor receptor (EGFR). It acts by inhibiting intracellular phosphorylation of the tyrosine kinase associated with the EGFR[1]. EGFR-TKIs are currently used in the treatment of a number of solid tumors. Various cutaneous side effects of EGFR-TKIs have been reported, including acneiform eruptions, chronic paronychia, xerosis, a seborrheic dermatitis-like eruption, changes in hair texture, and nonscarring alopecia[1]. The most common skin manifestation is a rash that has been described as a follicular or papulopustular eruption. However, significant or severe alopecia has rarely been reported in patients that receive EGFR-TKI monotherapy[1,2].

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CASE REPORT

A 61-year-old woman with metastatic non-small cell lung cancer (NSCLC) presented with erythematous erosive patches containing pustules on her scalp. She had been using 150 mg/day erlotinib (Tarceva®) for 11 months. Two months after starting drug administration, she experienced a mild acneiform facial eruption. By applying a topical macrolide, it improved after several days. However, about 9 months after taking the medicine, painful, erosive patches appeared on her scalp, which was accompanied by hair loss. Physical examination showed erythematous erosive patches with follicular pustules on the scalp (Fig. 1). No other adverse events were observed, including xeroderma or inflammation of the nails. A biopsy specimen taken from the scalp showed ruptured hair follicles and abundant perifollicular infiltrate with lymphocytes and neutrophils (Fig. 2). Bacterial and fungal stains were negative, but *Staphylococcus aureus* was cultured from the pustules. Routine laboratory investigation found no significant abnormalities.

Treatment with topical and oral steroids plus antibiotics was started and continued for 5 weeks. The dosage of erlotinib was decreased from 150 mg/day to 100 mg/day, and then the erythematous, pustular skin lesion gradually improved. However, an atrophic alopecic patch developed on her scalp (Fig. 3). The final diagnosis was cicatricial alopecia, and the alopecic lesion remained unchanged during a 9-months follow-up.

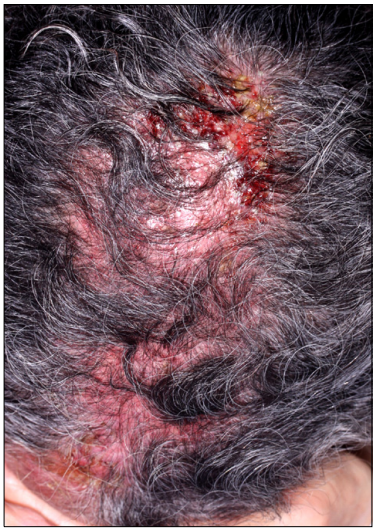

Fig. 1. Erythematous erosive patches containing follicular pustules on the scalp.

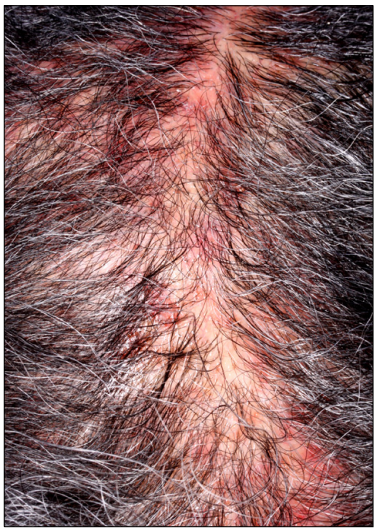

Fig. 3. Erythematous scarring, alopecic patches on the scalp.

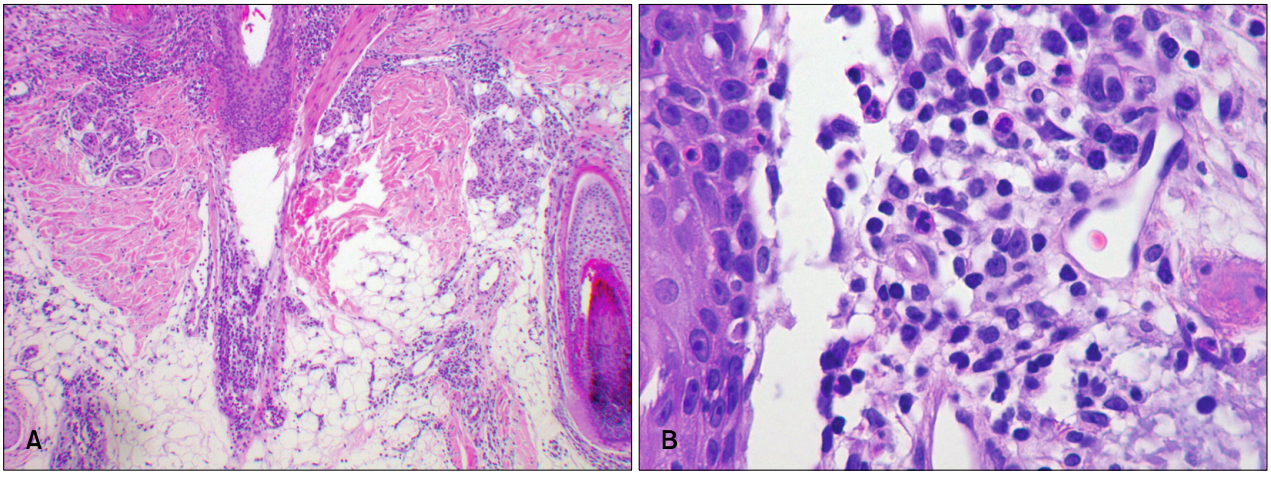

Fig. 2. (A) Skin biopsy from the scalp showing ruptured hair follicles (H&E, ×40). (B) Abundant perifollicular infiltrate with lymphocytes and neutrophils (H&E, ×200).

DISCUSSION

EGFR inhibitors have been approved for the treatment of NSCLC, pancreatic cancer, colorectal cancer and head and neck cancer[3]. Targeting the EGFR pathway with a small-molecule EGFR-TKI (erlotinib) or a monoclonal antibody (cetuximab) prolonged survival in patients with advanced disease in both the first- and second-line settings[4].

EGFR inhibitors can cause a range of adverse cutaneous reactions of variable severity. The most common skin toxicity is an acneiform or papulopustular rash that primarily affects the sebaceous areas of the scalp, face, and upper trunk. The rash can be itchy and, as a result, complicated by a secondary bacterial infection. The second most common skin toxicity affects the nails and includes symptoms such as discoloration, pitting, and paronychia[3]. Patients treated with EGFR inhibitors also sometimes exhibit hair abnormalities, like excessive eyelash and eyebrow growth or curly/wavy hair on the face or scalp that is both fine and brittle[2,3]. Substantial alopecia is uncommon. A literature search identified five other cases of alopecia associated with EGFR inhibitors; but, only one case of cicatricial alopecia was reported (Table 1)[1,2,5-7].

The mechanism underlying the folliculocentric rash remains unclear, although it is known that EGFR inhibitors can have several adverse effects on epithelial homeostasis. EGFR is strongly expressed in the basal layer of the epidermis, with lower expression in the lower dermal papilla, outer root sheath of the hair follicle, outer sheath

Table 1. Published English-language reports of alopecia associated with the use of EGFR inhibitors

Reference	Age	Sex	Diagnosis	Treatment	Characteristics
Pongpudpunth et al., 2009[1]	60	Female	Stage I NSCLC	Erlotinib 150 mg/d	Trichomegaly and alopecia
Costa et al., 2007[2]	74	Female	Stage IV NSCLC	Erotinib 150 mg/d	Alopecia
Donovan et al., 2008[5]	70	Female	Stage IV NSCLC	Genitinib 250 mg/d	Scaring alopecia
Graves et al., 2006[6]	65	Female	NSCLC	Genitinib	Inflammatory nonscaring allopecia
Robert et al., 2005[7]	Unknown	Female	Unknown	EGFR inhibitor	Frontal alopecia

EGFR: epidermal growth factor receptor, NSCLC: non-small cell lung cancer.

of the upper hair shaft, sebaceous glands, and eccrine sweat glands. Inhibiton of these EGFRs leads to growth and migratory abnormalities that result in a papulopustular rash and impaired differentiation[3,8].

Several studies have shown that EGFRs play an essential role in the maintenance of normal hair follicles. In 2002, Kimyai-Asadi and Jih[9] reported that a chimeric anti-EGFR antibody was toxic to follicles. EGFR-knockout mice had thin skin with poorly defined stratification and altered terminal differentiation of the epidermis and hair follicles. Failure of hair to enter the catagen stage resulted in a severe inflammatory reaction in the surrounding skin, follicular necrosis, and alopecia. In addition to its essential role in hair cycle regulation, EGFR also plays a role in regulating inflammation. This could be important to the pathogenesis of inflammatory infiltration and the destruction of hair follicles[6]. Based on these observations, the folliculocentric pustular rash was not considered to be the cause of infection; moreover, this hypothesis was supported by results obtained in microbiological cultures. The folliculocentric puspular rash is thought to result from abnormal keratinization, follicular retention and subsequent rupture of the affected hair follicle[10]. The present case exhibited erosive patches and pustules on the scalp, and *S. aureus* was cultured form the pustules. Histological findings showed folliculitis with an infiltrate of mixed inflammatory cells. We postulated that these findings were likely due to a secondary infection that resulted from abnormal keratinization of the hair follicles and a failure to control the inflammatory process due to EGFR inhibition.

During most of the hair cycle, the lower portion of the hair follicle is an immune-privileged site[6]. However, during follicle regression in the catagen stage, major histocompatibility complex class 1 antigens are expressed in the lower portion of the follicle, then activated macrophages infiltrate the area and the lower portion of the follicle degenerates[6]. EGFR induces suppression of free radical production, which might be necessary to control the inflammation process. Without this EGFR function, the expression of major histocompatibility complex class 1 antigens in the early catagen stage and the following inflammatory response could lead to the destruction of the hair follicle[6]. Thus, it is possible that cicatricial alopecia resulted from immune privilege failure in the hair follicle. Alternatively, development of cicatricial alopecia may result from various stimuli that induce the inflammatory infiltrate[11]. Possible antigenic stimuli include ultraviolet light in patients with discoid lupus erythematous in the scalp, certain medications in patients with lichen planopilaris, and *S. aureus* infection in patients with folliculitis decalvans[11]. In the case presented here, *S. aureus* may have aggravated the course of EGFR- induced cicatricial alopecia development.

Cicatricial alopecia caused by an EGFR inhibitor is relatively rare. Generally no bacteria are associated with follicular inflammation induced by treatment with an EGFR inhibitor. However, *S. aureus* was identified in this case. Histological findings indicated that *S. aureus* might have continued to break up follicular units and thus, aggravated inflammation. We hypothesized that these conditions might have caused cicatrical alopecia; however, accurate identification of the underlying mechanism requires further study.

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