Gefitinib-associated lichen planus pigmentosus-like eruption

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Abstract

The epidermal growth factor receptor (EGFR) signaling pathway is one of the oncogenic pathways in non-small cell lung cancer. Gefitinib is classified as a first-generation EGFR-tyrosine kinase inhibitor (TKI). A variety of cutaneous adverse effects related to the drug has been reported. Cutaneous hyperpigmentation is a rare side effect of EGFR inhibitor (EGFRi). Herein, we report a 62-year-old woman with non-small cell lung carcinoma who presented with symmetrical, slate-gray-to-brownish-black macular pigmentation on sun-exposed and non-sun-exposed areas after eight months of gefitinib administration. The clinical features were consistent with lichen planus pigmentosus. This case highlights the unusual hyperpigmented condition occurring in patients taking EGFR-TKIs.

Keywords: epidermal growth factor receptor, gefitinib, hyperpigmentation, inhibitor, lichen planus pigmentosus

Introduction

Cutaneous hyperpigmentation is a rare adverse effect of epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs). Herein, we describe a 62-year-old woman with slate gray hyperpigmentation after an eight-month course of gefitinib for non-small cell lung carcinoma

Case Synopsis

A 62-year-old woman presented with darkening of the skin on the face and neck, eight months into a course of gefitinib. Later, the rash gradually spread to the neck and torso. The hyperpigmentation was not preceded by any inflammatory changes. Her current medications were pravastatin, codeine, and betahistine. Pravastatin had been started 5 years before the onset of the cutaneous symptoms. Codeine and betahistine had been used irregularly for four months. Her topical products included 1% clindamycin lotion, sunscreen on the face and 10% urea cream. No hair dye had been used for more than 10 years.

On examination, multiple symmetrical, discrete and confluent, greyish, small and large macules and patches involving her forehead, lateral and posterior neck, v-area of the chest, upper back, and antecubital fossae were seen (**Figure 1**). Laboratory results were unremarkable. Skin biopsy specimen taken from the lesion at posterior neck showed band-like lymphohistiocytic infiltration and prominent pigmentary incontinence in the upper dermis. The overlying epidermis exhibited atrophy with focal vacuolar alteration (**Figure 2**).

Case Discussion

Gefitinib is classified as a first-generation EGFR-TKI. The mechanisms of action include binding to the EGFR, inhibiting the intracellular phosphorylation of

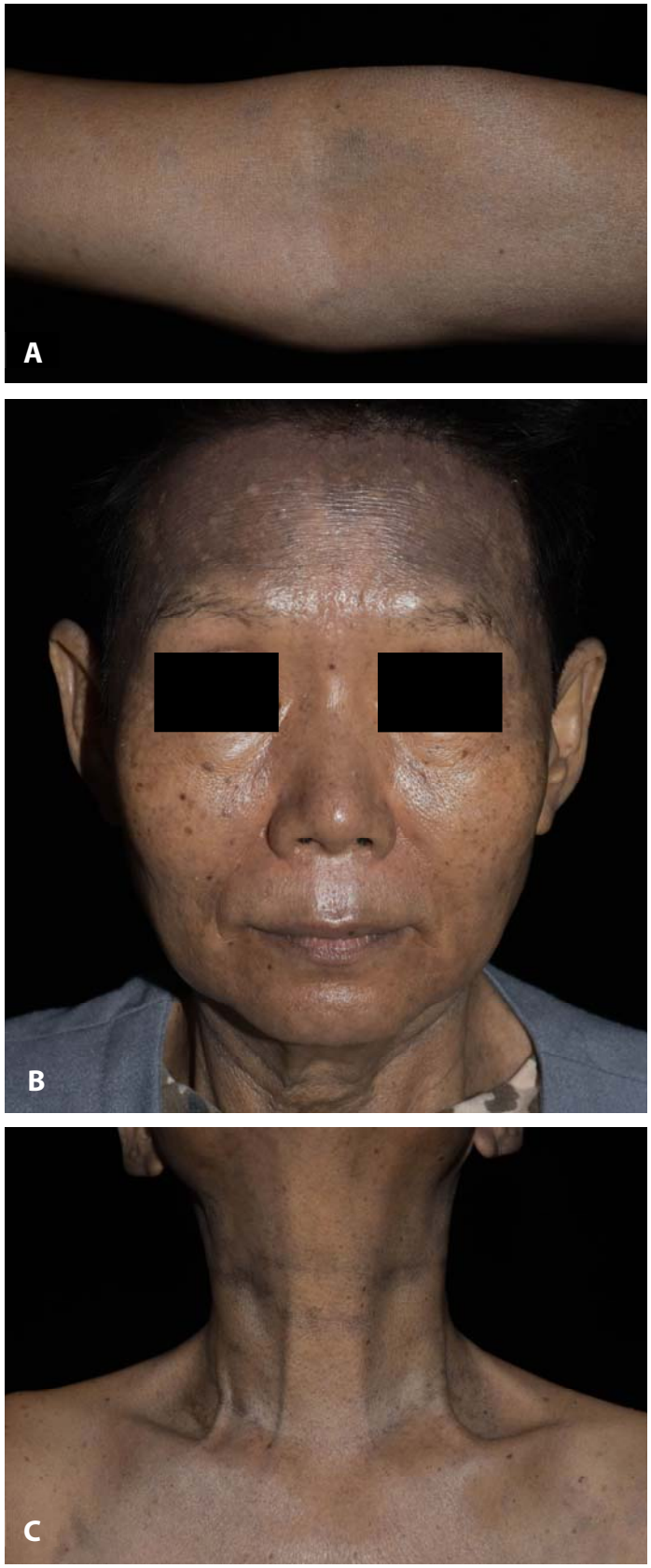

Figure 1. *Multiple slate-gray macules and patches were found on **A)** antecubital fossa, **B)** face and **C)** upper trunk.*

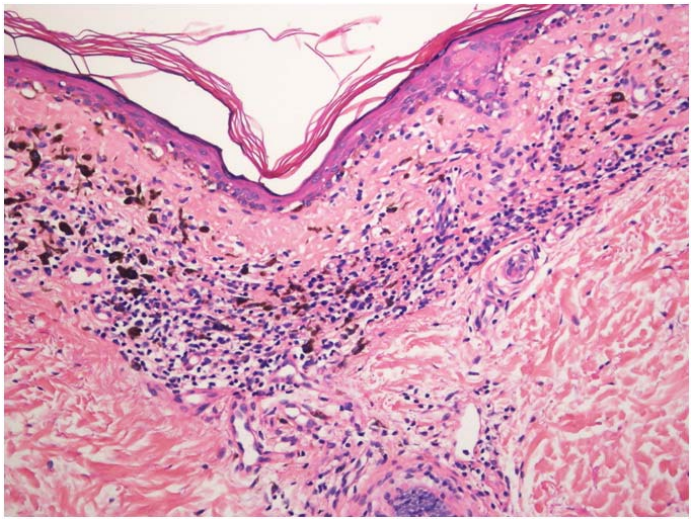

Figure 2. *Biopsy specimen from a lesion on the neck shows band-like lymphohistiocytic infiltration and prominent pigmentary incontinence in the upper dermis. There is atrophy in overlying epidermis with vacuolar alteration. H&E, 200×.*

tyrosine kinases, and then blocking the cancer growth [1]. Reported gefitinib side effects consist of a variety of cutaneous eruptions. However, hyperpigmentation is rarely reported [2]. We recently reported a case of ashy dermatosis (AD)-like hyperpigmentation induced by osimertinib, a selective inhibitor against EGFR with the T790M mutation [3].

Interestingly, besides cutaneous involvement, hyperpigmentation of the hair and eyebrows in a patient 7 months into gefitinib treatment has also been described [4]. In this case, dermoscopy revealed brown scalp hyperpigmentation in the affected hairy area. Moreover, reflectance confocal microscopy showed hair bulb bigeminy with pigmented keratinocytes. The authors speculated that the interrupt of SCF/c-kit signaling pathway by EGFR-TKIs might underlie these findings [4]. A summary of the previous reports of EGFR-TKI-induced pigmentary changes is presented in **Table 1**.

The clinical and histopathologic features of our patient fit well into the proposed global consensus for the diagnosis of lichen planus pigmentosus [5]. Pigmentary lesions gradually developed 8 months after the onset of gefitinib administration. The time interval is compatible with the average time of onset of drug-induced hyperpigmentation, that is 6.5

Table 1. *Summary of reported cases of EGFR inhibitor-induced pigmentary changes.*

Author, year	Age, gender	Cancer	Drug	Onset after the drug initiation	Morphology and distribution	Histopathology
Chang et al., 2004 [8]	43, female	Non-small cell lung carcinoma	Gefitinib	Months	Hyperpigmentation on the face, trunk, and legs occurred following the preceding acneiform eruptions	Basal layer hyperpigmentation and the dermal macrophages
Chang et al., 2004 [8]	60, female	Non-small cell lung carcinoma	Gefitinib	A few months	Multifocal hyperpigmentation occurred following the preceding acneiform eruptions	No data
Cosio et al., 2020 [4]	77, female	Basal cell carcinoma	Gefitinib	7 months	Hyperpigmentation of hair and eyebrows	No data
Lertpichitkul et al., 2020 [3]	71, female	Non-small cell lung carcinoma	Osimertinib	6 months	Slate grey hyperpigmentation, ashy dermatosis-like eruptions on the chest, buttocks, and forearms	Pigmentary incontinence in the upper dermis and vacuolar degeneration at the dermoepidermal junction
Our case	62, female	Non-small cell lung carcinoma	Gefitinib	8 months	Multiple slate grey macules and patches on the antecubital fossa, face and upper trunk	Band-like lymphohistiocytic infiltration and pigmentary incontinence in the upper dermis with focal vacuolar alteration

months [3,4]. The other current systemic drugs were used irregularly for a much longer time and despite stopping these drugs, there was further development of hyperpigmentation. Although patch and photo-patch tests were not done, there was no history of suspected allergens including hair dye. Moreover, the lesions were not limited to the areas in contact with the topical medications. Therefore, it is less likely for the contact substances to be a cause. Since gefitinib was required, it was not stopped. The hyperpigmentation was ongoing. A trial of topical 2% kojic acid cream produced a modest improvement.

Lichen planus pigmentosus is a rare entity that exhibits an acquired macular pigmentation of uncertain etiology (MPUE). Risk factors for lichen planus pigmentosus include viral infections (hepatitis C) and medications such as methadone, henna dyes, mustard oil, and homeopathic remedies [6,7]. It is characterized by diffuse, symmetrical, slate gray-to-brownish-black macular pigmentation. The lesions occur on sun-exposed and non-sun-exposed areas and the head and neck regions are the common areas of involvement [5]. The histopathology exhibits a lichenoid infiltration and melanophages on the superficial dermis. The first line treatment of lichen planus pigmentosus are topical corticosteroids and calcineurin inhibitors [6].

Conclusion

We herein reported an unusual case of gefitinib-associated lichen planus pigmentosus-like hyperpigmentation. It is interesting to note that the adverse events in the group of MPUE, namely AD and lichen planus pigmentosus, have been reported mainly in Asians, South Asians and Africans [5]. Dermatologists should be aware of this unusual

hyperpigmented condition occurring in patients taking EGFR-TKIs.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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