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Case Presentation

Erlotinib induced target-like purpura

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Abstract

Erlotinib is an epidermal growth factor receptor (EGFR) inhibitor, used as a treatment for advanced stage cancer. The most common side effect is cutaneous toxicity including the already known papulopustular reaction. We herein report a case of erlotinib induced target-like purpura, a peculiar cutaneous adverse event.

A 57-year-old patient with advanced non-small cell lung cancer was treated by erolotinib 150 mg daily. After taking the drug for three days, an unusual target-like purpura developed on her lower legs. Skin biopsy specimen taken from the lesion revealed an extravasation of erythrocytes in the upper dermis without destruction of blood vessel walls. This skin eruption cleared after the drug was withdrawn and recurred after erlotinib was re-challenged.

The mechanism underlying this cutaneous adverse event remains to be elucidated. Physicians should be aware of the rare side effect of this increasingly used drug.

Introduction

Erlotinib is an epidermal growth factor receptor (EGFR) inhibitor. It is used as a treatment for advanced stage cancer. The most common cutaneous toxicity is a papulopustular reaction [1, 2]. We herein report a case of erlotinib induced target-like purpura, a rare cutaneous adverse event.

Case synopsis

A 57-year-old woman presented with chronic cough, progressive dyspnea, and weight loss for 4 months. After extensive investigations, the diagnosis of non-small cell lung cancer with bone and liver metastasis was made. Her treatment was composed of palliative radiation therapy in combination with erlotinib 150 mg daily.

Three days after the medication was started, she noticed an erythematous eruption on her lower legs that gradually increased over a period of six weeks. Physical examination revealed multiple discrete purpuric macules with some target-like lesions that were interspersed with pustules on her lower legs, forearms, and buttock (Figure 1). In addition, generalized xerosis was also observed.

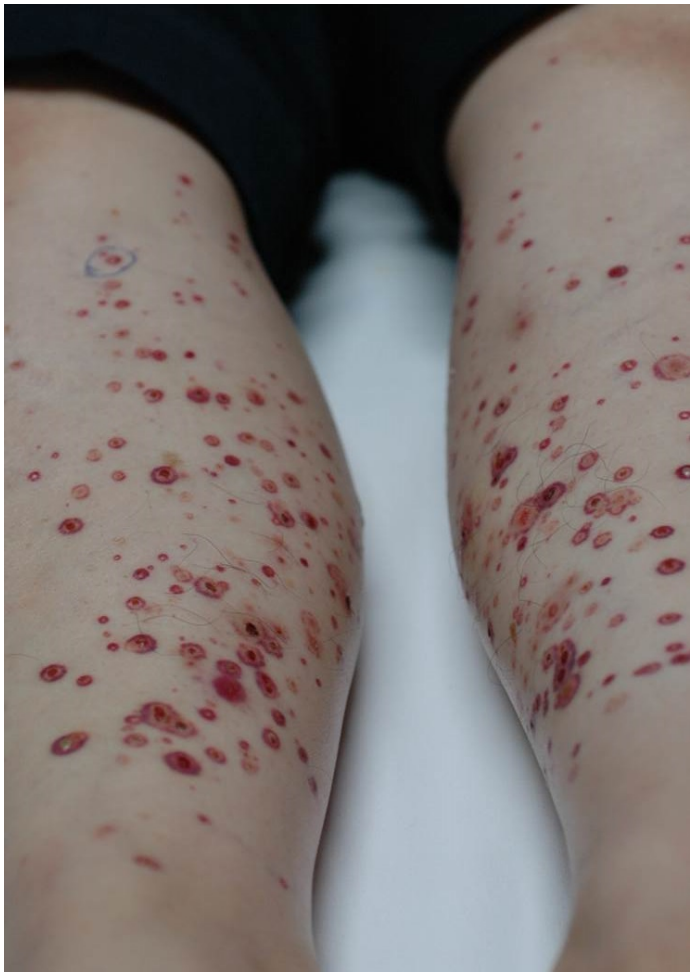

Figure 1. Purpuric macules and targetoid papules and small plaques

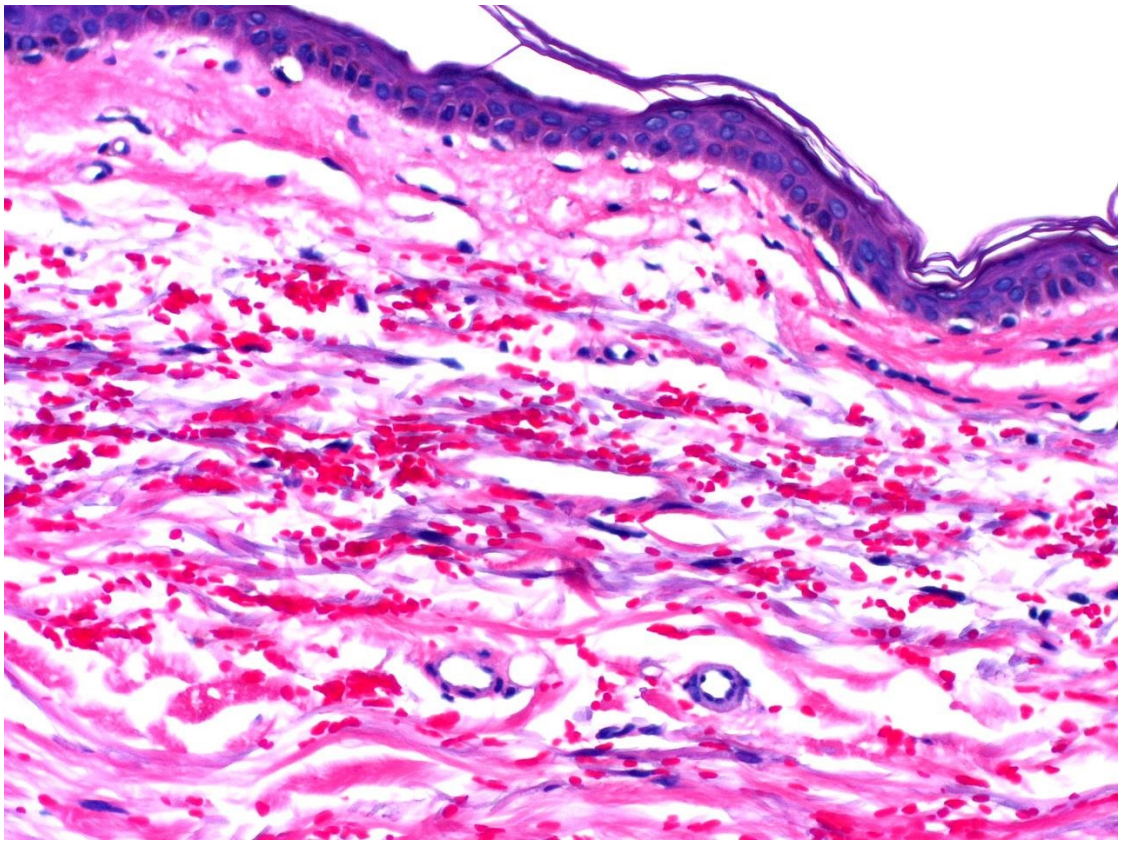

Figure 2. Extravasation of red blood cells in the upper dermis

The histopathological findings of the purpuric macules revealed an extravasation of erythrocytes in the upper dermis without destruction of blood vessel walls (Figure 2). Results of laboratory examination showed normal platelet counts, prothrombin time (PT) and partial thromboplastin time (PTT). Liver and renal function tests were within normal limits.

We hypothesized that the eruption occurred as a side effect of erlotinib. Therefore, the drug was stopped and topical fusidic acid ointment and 0.25% desoximetasone cream were applied twice daily. The skin eruption was significantly better after two weeks of the drug withdrawal and the use of topical medications. Erlotinib was then restarted at a lower dosage of 100 mg per day. Two months later, multiple purpuric macules on all extremities and trunk recurred, together with an acneiform eruption, paronychia, elongated irregular growth of eyelashes, and xerosis.

Discussion

Erlotinib is a tyrosine kinase inhibitor of a step in the epidermal growth factor receptor (EGFR) cascade. This particular pathway is essential for cell proliferation, migration, and angiogenesis [3, 4]. Papulopustular reaction is the most common side effect of EGFR inhibitors [1, 2]. This reaction occurs in a dose-dependent manner and is observed in 48 to 67% of patients taking erlotinib [5]. Moreover, the severity of the acneiform eruption is positively correlated with objective tumor response and prolongation of patient survival [2, 6]. The reaction usually occurs within 2 to 3 days of drug administration and peaks in 2 to 3 weeks [5, 7]. Other common cutaneous side effects include abnormal hair and/or eyelash growth, paronychia with/without pyogenic granuloma, xerosis, and telangiectasias [8].

In addition to papulopustular reaction, the patient developed target-like purpura. To our knowledge, there is only a single case report on erlotinib inducing purpura by Nakamura-Wakatsuki et al [9]. They reported a 79-year-old patient who was on erlotinib 150 mg daily as a treatment for adenocarcinoma of the lung. After the drug was used for a month, a papulopustular eruption and multiple asymptomatic purpuric macules developed on the lower legs and trunk. Histology of the skin specimen showed extravasation of red blood cells in the upper dermis. Despite the continuation of erlotinib, the purpuric lesions improved with residual pigmentation.

There are a few reports of another EGFR inhibitor, gefitinib, associated with vascular adverse events namely leukocytoclastic vasculitis [10, 11], livedo reticularis with retiform purpura [12], and purpura with petechiae [13, 14]. The clinical features are summarized in Table 1. However, the striking target-like purpuric eruption associated with erlotinib has not been described to our knowledge.

Table 1. The clinical features of the patients with gefitinib-associated vascular adverse events

	Uchimiya H et al[10]	Uchimiya H et al[10]	Fernández-Guarino M et al[11]	Blume JE et al[12]	Kurokawa I et al[13]	Sheen YS et al[14]	Sheen YS et al[14]	Sheen YS et al[14]
Age (years)	74	76	62	71	76	77	43	40
Sex	Female	Female	Male	Male	Female	Male	Female	Female
Race	Japanese	Japanese	Spanish	American	Japanese	Chinese	Chinese	Chinese
Malignancy	Lung cancer	Lung cancer	Carcinoma of the maxillar	Metastatic prostate cancer	Lung cancer	Lung cancer	Lung cancer	Lung cancer
Lag period* (months)	1	2	2	1	2.5	0.5	10	4
Clinical features	Palpable purpuric lesions and erosions on both legs	Multiple punctate purpuric lesions on both legs	Purpuric plaques with superficial desquamation on the legs	Diffuse livedo reticularis on the body and scattered retiform, purpuric, painful patches	Petechiae on the leg, ecchymosis on the buttock and pernio-like-lesion on the sole	Purpuric papules and erosions on the right leg	Erythematous papules, erosions, fissures and pustules on the legs	Erythematous papules and petechiae on the legs

Histology	Leukocytoclastic vasculitis	Leukocytoclastic vasculitis	Leukocytoclastic vasculitis	Vacuolar change of basal layer, hemorrhage, superficial dermal vascular congestion, no vasculitis	Leukocytoclastic vasculitis	Subcorneal pustule and epidermal atrophy	Subcorneal pustule, telangiectasia and extravasation of red blood cells	n/a**
Treatment	Stopped gefitinib	Stopped gefitinib	Stopped gefitinib	Stopped gefitinib Local wound care measures	Stopped gefitinib Betamethasone 2 mg/day orally	Continued gefitinib Clobetasol propionate, 0.05%, ointment	Stopped gefitinib Clobetasol propionate, 0.05%, ointment	Continued gefitinib Clobetasol propionate, 0.05%, ointment
Clinical course	Healed in 2 weeks	Healed in 17 days	Healed in 3 weeks	Healed in 6 weeks	Healed with pigmentation in 8 days	Healed in 2 weeks	Healed in 17 days	Healed in 2 weeks
Rechallenge	Yes, did not recur	Yes, did not recur	Not done	Not done	Not done	n/a**	Not done	n/a**

*Lag period: duration between gefitinib initiation and the beginning of vascular adverse symptoms, **n/a: not applicable

The exact mechanism of EGFR inhibitor induced vascular adverse events is still unknown. EGFR is normally expressed on basal layer of the epidermis, outer root sheath of the hair follicles, sebaceous and eccrine epithelium, dendritic antigen-presenting cells, various connective tissue cells, and notably, some endothelial cells [15, 16]. Consequently, the disruption in normal EGFR pathway may give rise to abnormal vascular formation and impairment of blood vessels walls. These then lead to red blood cells extravasation and purpuric eruption ensues [11].

In conclusion, we report a case of erlotinib causing targetoid purpura. This is a rare cutaneous side effect of the drug. Despite the adverse event, the patient will likely be able to use erlotinib together with topical treatment. Hence this is not considered to be a drug-limiting side effect. Physicians should be aware of the wide range of cutaneous toxicity of this relatively new chemotherapeutic agent. Further studies regarding treatment of these reactions are warranted.

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