Symmetrical drug-related intertriginous and flexural exanthema secondary to epidermal growth factor receptor inhibitor gefitinib

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INTRODUCTION

Gefitinib, an epidermal growth factor receptor (EGFR) inhibitor, has been associated with several cutaneous side effects.[1] We report a patient presenting with symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) associated with gefitinib treatment for stage IV non–small cell lung cancer.

Abbreviations used:

EGFR: epidermal growth factor receptor
SDRIFE: symmetrical drug-related intertriginous and flexural exanthema

CASE

A 72 year-old woman known for having lung adenocarcinoma metastatic to the brain presented to the emergency department for a 2-month history of a severe skin eruption involving the gluteal, inguinal, axillary, and inframammary areas. The lesions were pruritic and became significantly more painful over the week preceding her presentation to the emergency department. No systemic symptoms were reported. The patient was started on gefitinib, a tyrosine kinase inhibitor of EGFR, 4 weeks before the onset of the eruption.

Examination found well-defined V-shaped erythema of the gluteal and inguinal/perigenital areas extending to the medial thighs symmetrically. The inframammary and axillary folds presented a similar erythematous eruption bilaterally. Red satellite lesions, purulent discharge, and honey-colored crusting suggested secondary infection of the eruption (Fig 1).

Medical and dermatologic history

The patient had stage IV non–small cell lung cancer diagnosed 9 months before presentation. Medical history includes a remote history of breast cancer surgically resected in 1987. Her dermatologic history was notable for a remote episode of shingles. In addition, during a previous hospitalization, the patient had a documented allergic reaction to amoxicillin, which caused a generalized erythematous eruption that resolved 2 weeks after the discontinuation of the antibiotic. Medications before the initiation of gefitinib treatment included levothyroxine.

Histopathology and skin cultures

The skin biopsy results showed extensive dermal inflammatory infiltrate, mainly composed of lymphocytes, neutrophils, and eosinophils, with prominent papillary dermal edema and minimal epidermal changes, consistent with a drug eruption (Fig 2). Culture of skin swabs found growth of *Klebsiella* spp., *Enterococcus* spp., and *Candida albicans*.

Laboratory data

Laboratory values at the time of admission were significant only for electrolyte abnormalities (potassium, 2.4 mmol/L; magnesium, 0.65 mmol/L; phosphate, 0.55 mmol/L). Results of a complete blood

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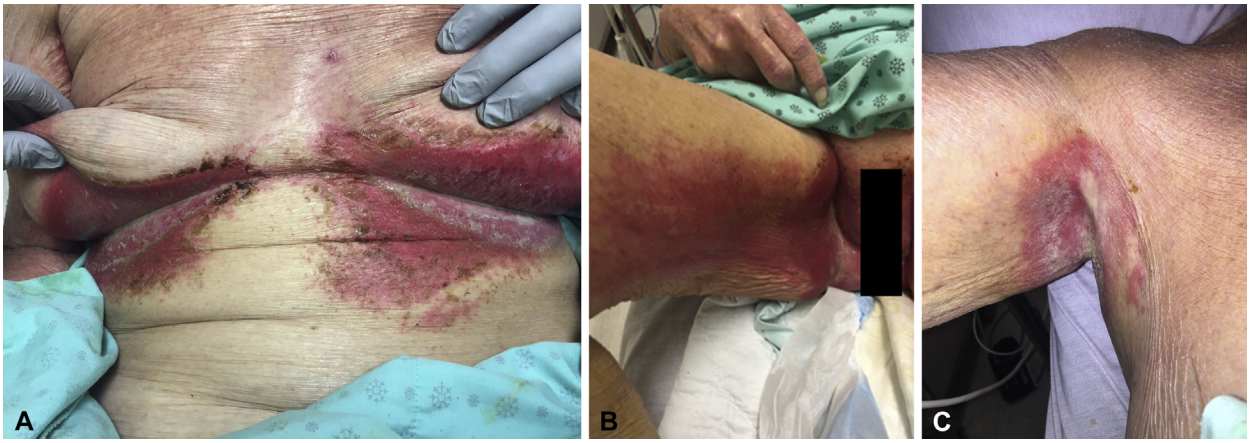

Fig 1. Erythematous plaques with honey-colored crust and green discharge over the inframammary areas (**A**), inguinal fold and medial thigh (**B**), and axial folds bilaterally (**C**). The eruption started four weeks after the beginning of gefitinib. Culture showed growth of *Klebsiella* spp., *Enterococcus* spp., and *Candida albicans*.

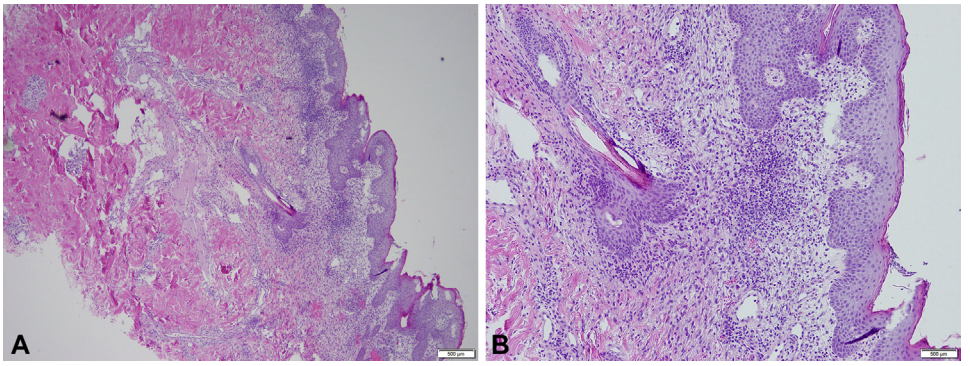

Fig 2. **A** and **B**, Histopathology findings show extensive dermal inflammatory infiltrate, mainly composed of lymphocytes, neutrophils, and eosinophils with prominent papillary dermal edema and minimal epidermal changes, consistent with a drug eruption.

count, hepatic function panel, and a venous blood gas were all within normal limits.

Treatment and evolution

At presentation, gefitinib was stopped, and the patient was initially treated with silver sulfadiazine cream, ciclopirox olamine cream, and oral fluconazole with only mild improvement. The patient improved significantly after being treated with oral dexamethasone, 8 mg twice a day for 1 week, which was then tapered over 2 weeks, and topical hydrocortisone 1% cream twice a day (Fig 3).

Given the progression of the cancer and lack of alternative treatment, the oncologist decided to restart gefitinib after 4 weeks of discontinuation with close monitoring. The intertriginous and flexural exanthems flared after 1 week of treatment, which confirmed gefitinib to be the causative agent. Concomitant to the flexural exacerbation, the patient also developed new papulopustular lesions on the cheeks, chest, and lower extremities, an eruption commonly associated with gefitinib.[2] These lesions were accompanied by dry eyes and alopecia, a constellation of symptoms consistent with PRIDE syndrome (papulopustules and/or paronychia, regulatory abnormalities of hair growth, itching, dryness due to EGFR inhibitors).[3] Gefitinib was stopped once again because of worsening of the flexural erythema.

DISCUSSION

The term *baboon syndrome* was originally presented in 1984 to describe a cutaneous reaction brought on by systemic exposure to mercury vapors (ie, via inhalation) in patients with a known previous cutaneous sensitization, usually with mercury-containing topical preparations.[4] The authors described a characteristic pattern of diffuse

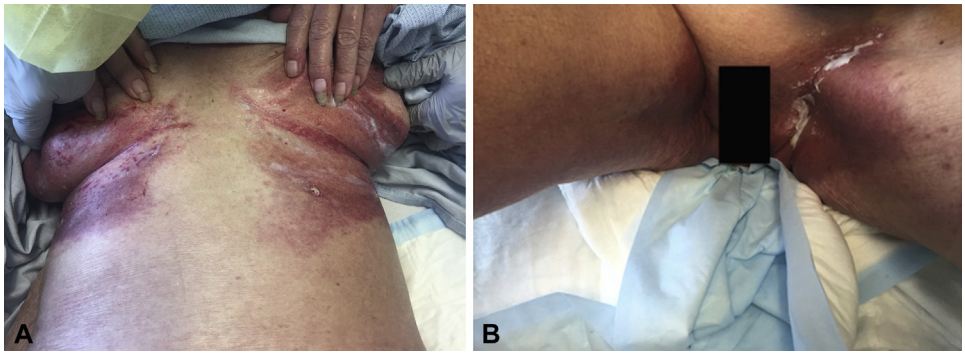

Fig 3. Improvement 2 weeks after discontinuation of gefitinib and treatment. Postinflammatory hyperpigmentation and erythema with erosions over the inframammary areas (**A**) and violaceous erythema over the inguinal folds and medial thighs (**B**).

erythema of the buttocks extending to the upper inner surface of the thighs, associated with erythema of the axillae.

Häusermann et al[5] coined the acronym *SDRIFE* to further define the subset of cases of baboon syndrome manifesting the characteristic eruption after systemic absorption of medications, in the absence of a known history of previous cutaneous sensitization. The proposed criteria for SDRIFE feature (1) exposure to a systemically administered drug at first or repeated dose (excluding contact allergens), (2) sharply demarcated erythema of the gluteal/perianal area and/or V-shaped erythema of the inguinal/perigenital area, (3) involvement of at least one other intertriginous/flexural localization, (4) symmetry of affected areas, and (5) absence of systemic involvement.[5]

It is worth noting that although the criteria by Häusermann et al[5] criteria require the absence of a reported history of cutaneous sensitization, the diagnosis does not require or predict a negative patch test per se. In fact, patch tests serve an equivocal purpose in the diagnosis of SDRIFE, as less than half of cases will test positive.[6,7] Prick testing result is negative in most cases of SDRIFE.[6] Drug provocation tests are the gold standard for determining the offending agent.[6,7]

In addition to well-demarcated erythema in the flexures, SDRIFE may present with small papules, pustules, and vesicles overlying the erythema.[5,8] The eruption spares the face, palms, soles, and mucosa.[5] Multiple drugs have been associated with SDRIFE, namely, amoxicillin,[4] penicillin,[9,10] valacyclovir,[11] risperidone,[12] and infliximab.[13]

Our patient meets the five criteria for SDRIFE, and recurrence of the eruption after re-exposure to gefitinib confirms that it is the causative agent. In this case, a patch test was not performed, as it would have been redundant in the context of a repeated reaction following re-exposure.

The approval of gefitinib as a first-line agent for metastatic non–small cell lung cancer by the US Food and Drug Administration[14] will undoubtedly lead to the growing use of this agent. As such, increased awareness of SDRIFE as a potential cutaneous adverse drug reaction to this type of EGFR inhibitor is essential.

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