Letter to the Editor

Painful Annular Pustular Drug Eruption Induced by Erlotinib in a Patient With Non–Small Cell Lung Cancer

To the Editor:

Erlotinib, similar to gefitinib, is an oral low-molecular-weight inhibitor of tyrosine kinase associated with the epidermal growth factor receptor (EGFR). Both drugs reversibly inhibit the activation of EGFR tyrosine kinase through competitive binding of the adenosine triphosphate–binding domain of the receptor. Erlotinib has been approved for prolonging survival in patients with non–small cell lung cancer (NSCLC) after first- or second-line chemotherapy.

A 54-year-old woman presented to the dermatology department with a generalized painful pustular drug reaction of 4 weeks' duration. She was diagnosed with advanced NSCLC (T4N0M1) 12 months prior to this visit. Chemotherapy commenced with first-line chemotherapeutic agents on a 3-week schedule, including cisplatin 80 mg/m^2 intravenously on day 1 plus gemcitabine hydrochloride 1200 mg/m^2 on days 1 and 8 of a 21-day cycle, combined with bevacizumab 15 mg/kg every 3 weeks. Later, after 4 courses of conventional chemotherapy, she experienced poor control of her malignancy because of frequently missing scheduled chemotherapy for hematologic toxicity, such as leukopenia, thrombocytopenia, bleeding tendency, and nasal bleeding. She started a new target therapy with oral erlotinib 150 mg daily and continued with bevacizumab at the initially prescribed dose of 15 mg/kg every 3 weeks. The first-line chemotherapy agents cisplatin and gemcitabine were stopped. However, 7 months later after persistent therapy with erlotinib and bevacizumab, a severe painful erythematous maculopapular skin rash and desquamation with annular pustular eruption presented on the trunk and limbs, more seriously on both lower extremities (Figures 1A and 1B), as well as some scattered follicular papules on the chest and both shoulders (Figure 1C). A skin biopsy from the annular pustular eruption demonstrated patchy subcorneal

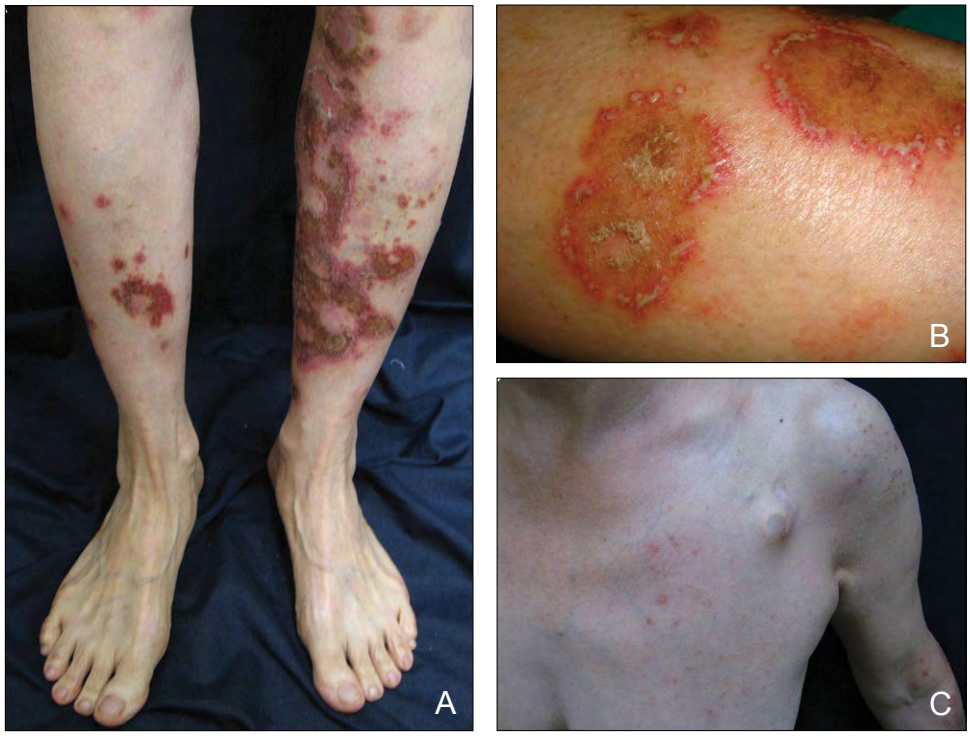

Figure 1. A painful erythematous maculopapular skin rash with confluence on both lower legs was demonstrated (A) with an annular pustular eruption (B). Scattered follicular papules were found on the chest and shoulder (C).

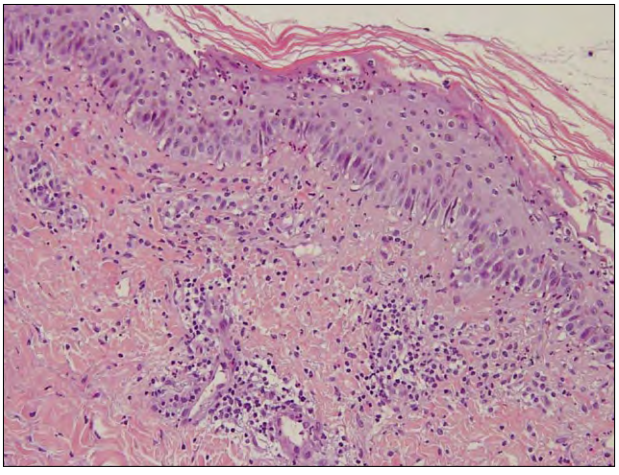

Figure 2. Pustular erythroderma demonstrated interface dermatitis and subcorneal neutrophilic-rich pustules, numerous neutrophilic/eosinophilic exocytosis with some keratinocyte apoptosis, a perivascular infiltrate of lymphohistiocytic cells, and neutrophil infiltrations (H&E, original magnification ×200).

neutrophilic pustules with a background of spongiosis and neutrophilic/eosinophilic exocytosis. Basal cell vacuolar change and keratinocyte apoptosis were present with a perivascular infiltrate of mixed lymphohistiocytic cells and neutrophils in the superficial dermis (Figure 2). According to these histopathologic features and a literature review, severe annular pustular drug eruption induced by erlotinib (grade 3 skin toxicity [>50% body surface area]) was confirmed. The patient ceased erlotinib usage temporarily and received treatment with systemic and topical corticosteroids, moisture cream, and analgesics. The skin lesions improved 4 weeks later. Thereafter, she restarted erlotinib from a low dose and tolerated it well.

The most common side effects of erlotinib are cutaneous adverse effects (eg, acneform eruption, xerosis, fissures of the palms and soles and paronychia, nasal or oral ulcers, urticarial rash, seborrheic dermatitis) and diarrhea in 75% (43/57) and 56% (32/57) of patients, respectively.[1] However, because these secondary effects respond well to treatment, few patients discontinue erlotinib specifically. In the presence of skin rash, dose reductions to subtherapeutic levels are claimed to remain effective and prevent unnecessary early treatment termination.[2] In general, the skin rash manifests within 1 to 3 weeks after initiation of the anti-EGFR drugs and is maximal by the third to fifth week. A dose-related adverse reaction generally is observed, with higher incidence and more severe rash encountered at higher-dose levels.[3] However, in our patient, the painful annular pustular rash appearing after long-term administration of erlotinib (7 months) is uncommon. This unusual presentation of late-onset cutaneous adverse reaction mimicking superficial dermatophytosis rarely has been reported and should not be misdiagnosed as a fungal infection. Periodic acid–Schiff staining and tissue cultures can be undertaken to help in the differential diagnosis.[4]

The Akt protein kinase family (also known as protein kinases B) is a predominantly cytoplasmic serine-threonine kinase that is activated by phosphorylation in response to growth factors or insulin. In humans, there are 3 isoforms in the Akt protein family: *AKT1* (v-akt murine thymoma viral oncogene homdog 1), *AKT2*, and *AKT3*. *AKT1* is involved in cellular survival pathways by inhibiting apoptotic processes and has been implicated as a major factor in many types of cancer. It also is able to induce protein synthesis pathways and plays a major role in cell metabolism and growth.[5] *AKT1* has been known to provide an essential survival signal required for differentiation and stratification of primary human keratinocytes.[6] Tan et al[7] identified that higher baseline Akt activity in normal keratinocytes is significantly correlated with not developing a rash (P=.0017). Low skin Akt activity, as a negative predictor, may help to identify the patients who are more likely to develop skin toxicity from erlotinib and possibly from other anti-EGFR agents.

However, cutaneous toxicity seems to be a surrogate marker of clinical benefit, with patients who present with more severe skin rash having a better response to treatment and long survival.[1] Prior studies found a positive correlation between the degree of rash and the months of survival in patients treated with cetuximab.[8,9] In one study, erlotinib, similar to cetuximab, was suggested to have a better response to treatment in patients with more severe cutaneous toxicity.[1]

In a study of EGFR target therapy with cetuximab, skin toxicity significantly (P=.03) increased when added to the first-line chemotherapy and bevacizumab, a kind of vascular endothelial growth factor inhibitor. The increase of skin toxicity in the cetuximab-containing treatment group could be fully attributed to cetuximab-related skin toxicity.[10] Erlotinib resistance may be associated with a rise in host stromal and tumor cell vascular endothelial growth factor. The multitargeted agent approach, including a combination of single-targeted therapies, is the next generation of targeted therapies in solid tumors. Our patient concomitantly used bevacizumab, which is a vascular endothelial growth factor–targeted agent that is widely used in general oncology

practice, every 3 weeks. The combined inhibition of both vascular endothelial growth factor and EGFR signaling pathways has the clinical potential to offer additional benefits in preclinical and early clinical data for treatment of NSCLC. It is well-tolerated and has demonstrated encouraging efficacy and safety in early clinical studies.[11]

We present a rare case of a painful annular pustular drug eruption induced by erlotinib treatment of NSCLC. This late-onset cutaneous side effect of anti-EGFR drugs mimicking superficial dermatophytosis should not be misdiagnosed as a fungal infection. Erlotinib resistance and multitargeted agent therapy are related topics that merit further investigation. Bevacizumab, a kind of vascular endothelial growth factor inhibitor that may delay wound healing, would play an important role. It has not been determined if bevacizumab deteriorates the skin toxicity of erlotinib in a patient with NSCLC. Because multitargeted agent therapy has become frequently used, physicians need to be familiar with its severe cutaneous adverse effects.

Sincerely,
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The authors report no conflict of interest.

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