Acneiform Eruptions Induced by Epidermal Growth Factor Receptor Inhibitors: Treatment With Oral Isotretinoin

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The most common cutaneous side effects to epidermal growth factor receptor (EGFR) inhibitors are follicular or acneiform eruptions, nail disorders, xerosis, and desquamation. Although topical and oral antibiotics with or without topical corticosteroids usually are safe and effective treatment options for acneiform eruptions due to EGFR inhibitors, they are not always successful in refractory cases. We report 3 cases of severe acneiform eruptions induced by EGFR inhibitors that were successfully treated with oral isotretinoin. Complete response was observed in all 3 patients. We recommend oral isotretinoin for the management of acneiform reactions to EGFR inhibitors when the lesions persist or worsen despite antibiotic treatment.

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Cutaneous side effects to epidermal growth factor receptor (EGFR) inhibitors have become well-known among dermatologists, as these drugs are widely used for the management of many solid tumors, particularly those affecting the gastrointestinal tract.[1-3] Cutaneous side effects presumably are linked to the function of EGFR in epithelial development and are considered the most common adverse reactions to EGFR inhibition. The growing investigation and use of EGFR inhibitors in antitumor therapy has been originated in their specificity for EGFR, which improves their ability to target cancer cells and their safety profile compared to other conventional chemotherapeutic agents.[4-8]

Dermatologists must be familiar with the cutaneous side effects typically seen in patients taking EGFR inhibitors and also must be able to treat the side effects with confidence. Successful management of these side effects will greatly contribute to improved adherence to treatment and more effective cancer management. The most common cutaneous side effects to EGFR inhibitors are follicular or acneiform eruptions, nail disorders, xerosis, and desquamation.[9] Topical and oral antibiotics with or without topical corticosteroids usually are a safe and effective treatment option for EGFR inhibitor–induced acneiform eruptions.[9,10] In most patients, early initiation of treatment is sufficient to prevent dose reductions or discontinuation of anti-EGFR therapy. In rare cases in which antibiotics and corticosteroids fail to clear the lesions, oral isotretinoin may be used.[11-13]

We report 3 cases of patients who received anti-EGFR therapy and developed severe acneiform eruptions that did not respond to conventional treatment. They were successfully treated with oral isotretinoin.

Case Reports

Patient 1—A 77-year-old man being treated with cetuximab was referred to the dermatology department by the oncology department because of an acneiform eruption on his face and back of 1 month's duration. He had been diagnosed with metastatic colorectal adenocarcinoma that was treated with surgery and polychemotherapy 3 years prior to presentation. He had recently been started on weekly

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cetuximab therapy due to disease progression. Nine days after the first administration of cetuximab he developed an acneiform eruption on his face and back that became worse with each new infusion. Physical examination showed papules, nodules, and pustules on the face and back. *Staphylococcus epidermidis* was isolated in a culture of the pustular lesions. Systemic antibiotic therapy was initiated with oral doxycycline monohydrate 100 mg daily and topical clindamycin for 1 month. Although the facial lesions improved, those on his back did not improve, which led to the addition of topical erythromycin to doxycycline therapy for another month. However, the lesions on the back persisted (Figure 1A) and oral isotretinoin 10 mg daily was administered. The patient showed remarkable improvement after 1 month, and the lesions resolved completely within 2 months (Figure 1B). Treatment was continued for 5 more months with no side effects. Three months later, however, the eruption recurred and treatment with isotretinoin was restarted.

Patient 2—A 70-year-old woman being treated with cetuximab for peritoneal metastasis of a colorectal carcinoma was referred to the dermatology department because of a grade 3 (severe) acneiform eruption (according to the National Cancer Institute Common Toxicity Criteria) of 5 weeks' duration that mainly affected her face. She had been treated with oral doxycycline monohydrate 100 mg daily and topical steroids and antibiotics for 1 month without response (Figure 2A). The eruption was considered to be a dose-limiting toxicity and a reduction in the cetuximab regimen was proposed. However, the patient's excellent response to cetuximab prompted us to first try treatment with oral isotretinoin 20 mg daily. Complete response was achieved after 1 month of therapy (Figure 2B), and treatment was tolerated for another 3 months without side effects.

Patient 3—A 65-year-old man being treated with erlotinib was referred to the dermatology department from the oncology department with an acneiform eruption affecting the face and trunk of 1 month's duration. He had been diagnosed with metastatic lung adenocarcinoma 1 year prior and had received treatment with carboplatin and gemcitabine. Treatment was interrupted because of hematologic activity, and erlotinib was initiated. One month later the patient developed an acneiform eruption on his face and trunk. Physical examination showed a pustular, papular, nodular eruption at both sites. Systemic antibiotic therapy was initiated with oral doxycycline monohydrate 100 mg daily and topical clindamycin for 1 month. Although some improvement was observed in the facial lesions, treatment with oral doxycycline was continued for an additional 4 months with an incomplete response (Figure 3A). Oral isotretinoin 10 mg daily was administered. The patient showed a clear improvement and the lesions completely resolved within 2 months (Figure 3B). Treatment was continued for an additional 6 months with no side effects observed.

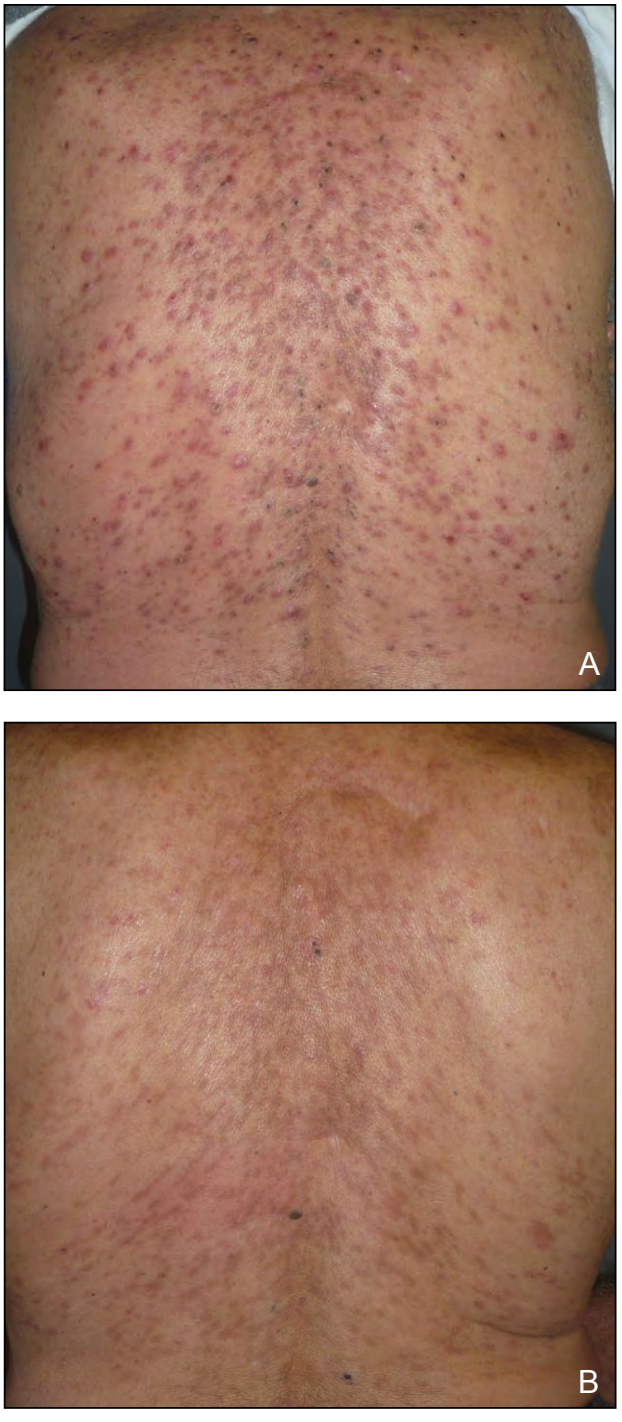

Figure 1. Patient 1 with an acneiform eruption from cetuximab therapy. Lesions on his back did not improve after 2 months of oral doxycycline treatment (A). After 2 months of treatment with oral isotretinoin, the lesions resolved completely (B).

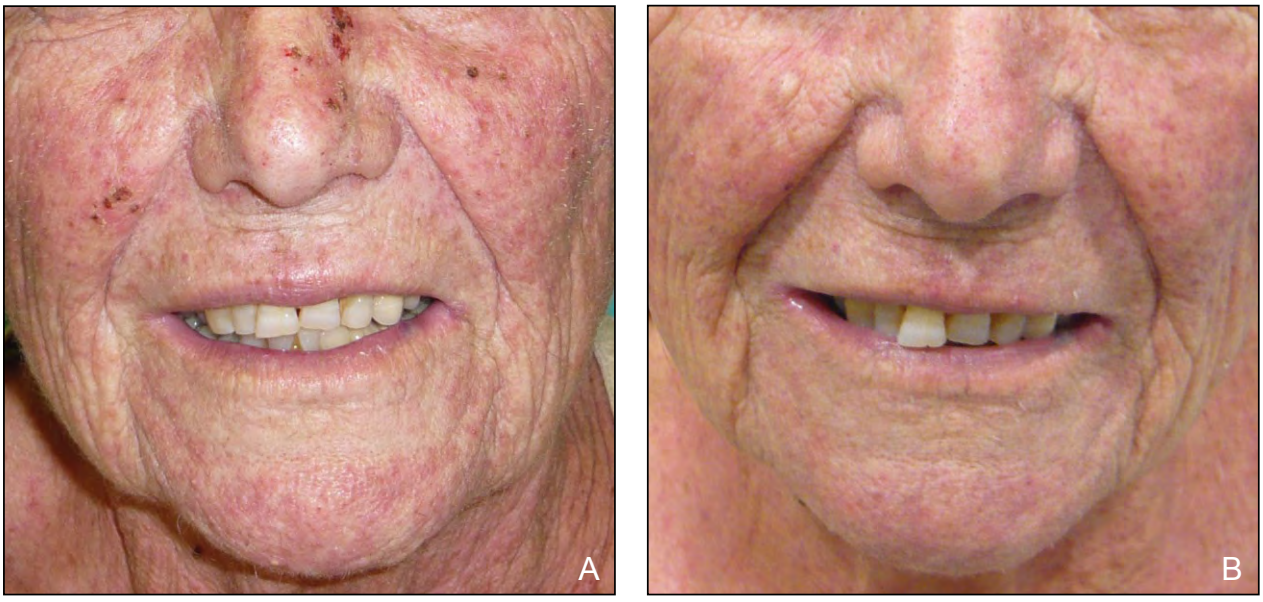

Figure 2. Patient 2 with an acneiform eruption from cetuximab therapy. Lesions on the face did not respond to 1 month of treatment with oral doxycycline monohydrate and topical steroids and antibiotics (A). Complete response was achieved after 1 month of treatment with oral isotretinoin (B).

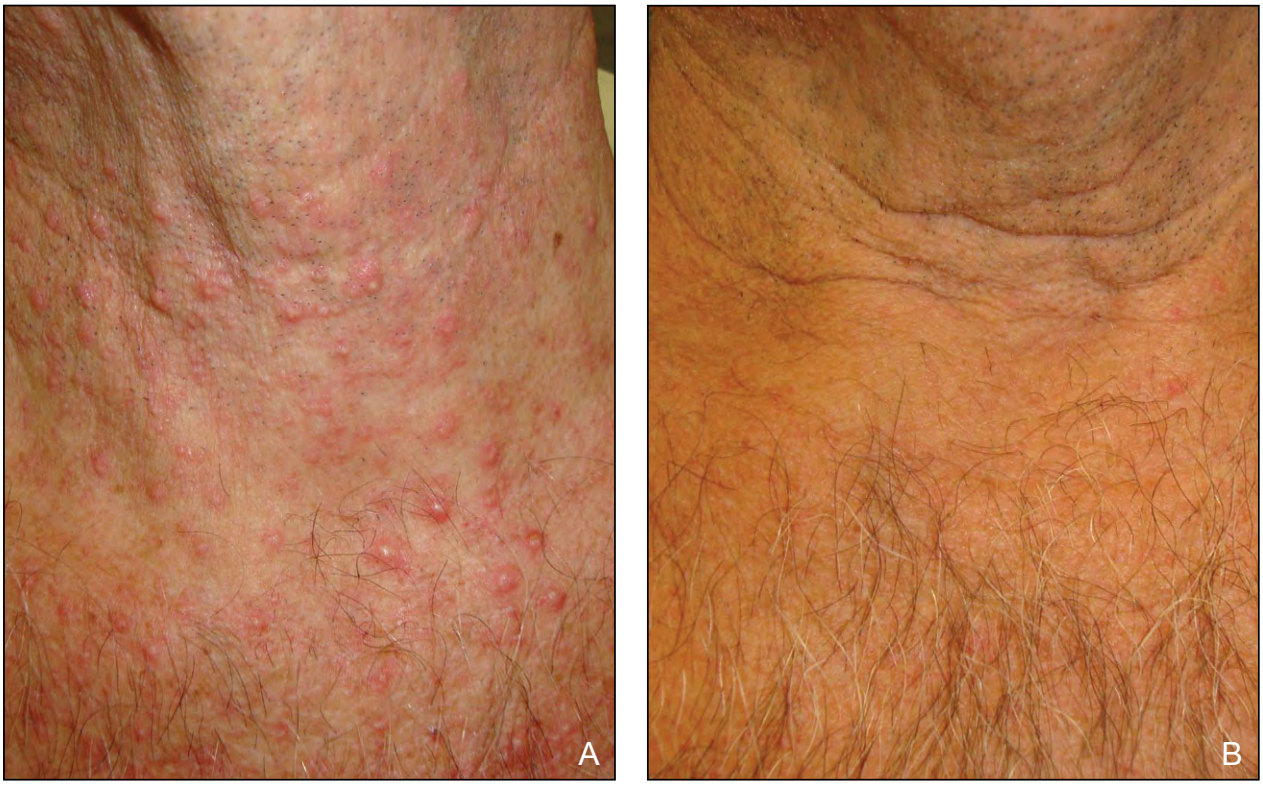

Figure 3. Patient 3 with an acneiform eruption from erlotinib therapy. There was an incomplete response after treatment with oral doxycycline (A). Complete resolution was achieved after 2 months of treatment with oral isotretinoin (B).

Comment

Cutaneous toxicity is the most evident adverse effect of EGFR inhibitors because EGFR is expressed in the epidermis, the sweat gland apparatus, and the hair follicle epithelium. The use of EGFR inhibitors likely prevents hair follicles from entering the catagen phase and causes defects in the follicular outer root sheath, possibly inducing follicular rupture and

an inflammatory perifollicular reaction. The precise mechanism by which inhibition of EGFR leads to acneiform eruptions is unknown; therefore, the management of these lesions remains controversial.

Typically, acneiform eruptions due to EGFR inhibitors involve the face and upper trunk, but they can sometimes extend to the extremities and the lower back. Although the eruption typically manifests as papules and pustules, inflammatory nodules may be seen but not often. As demonstrated in our patients, time to onset is short, with lesions usually appearing within several days of treatment.

In our experience, topical antibiotics such as erythromycin and clindamycin are useful for the management of mild acneiform eruptions due to EGFR inhibitors. For patients with moderate eruptions, we use oral doxycycline monohydrate 100 mg once or twice daily in addition to topical treatment for 1 or 2 months. We have observed that the intensity of the eruption increases during the initial infusions of the inhibitor but usually decreases 2 or 3 months later, which may explain the improvement of the eruption in patients 2 and 3 even after we stopped isotretinoin. In severe cases or in cases in which the eruption persists or worsens despite antibiotics, oral isotretinoin can be used.[11-13]

Conclusion

We have described 3 cases in which treatment with isotretinoin resulted in rapid resolution of lesions from an acneiform eruption to EGFR inhibitor therapy. In 1 case (patient 1), isotretinoin had to be reintroduced because of recurrence. In our experience, isotretinoin is useful for the treatment of refractory acneiform eruptions because it allows patients to continue receiving treatment of their cancer.

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