

Thalidomide Analogue Drug Eruption Along the Lines of Blaschko

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PRACTICE POINTS

- Dermatologists should be aware of the variety of cutaneous adverse events that can arise from the use of immunotherapeutic agents for hematologic malignancies.
- Some cutaneous reactions to immunotherapeutic medications, such as pityriasiform eruption and blaschkitis, generally are benign and may not necessitate halting an important therapy.

To the Editor:

Lenalidomide is a thalidomide analogue used to treat various hematologic malignancies, including non-Hodgkin lymphoma, myelodysplastic syndrome, and multiple myeloma (MM).¹ Lenalidomide is referred to as a degrader therapeutic because it induces targeted protein degradation of disease-relevant proteins (eg, Ikaros family zinc finger protein 1 [IKZF1], Ikaros family zinc finger protein 3 [IKZF3], and casein kinase I isoform- α [CK1 α]) as its primary mechanism of action.^{1,2} Although cutaneous adverse events are relatively common among thalidomide analogues, the morphologic and histopathologic descriptions of these drug eruptions have not been fully elucidated.^{3,4} We report a novel pityriasiform drug eruption followed by a clinical eruption suggestive of blaschkitis in a patient with MM who was being treated with lenalidomide.

A 76-year-old man presented to the dermatology clinic with a progressive, mildly pruritic eruption on the chest and axillae of 1 year's duration. He had a

medical history of chronic hepatitis B, malignant carcinoid tumor of the colon, prostate cancer, and MM. The eruption emerged 1 to 2 weeks after the patient started oral lenalidomide 10 mg/d and oral dexamethasone 40 mg/wk following autologous stem cell transplantation for MM. The patient had not received any other therapy for MM.

Physical examination revealed multiple erythematous, hyperpigmented, scaly papules and plaques on the lateral chest and within the axillae (Figure 1). A skin

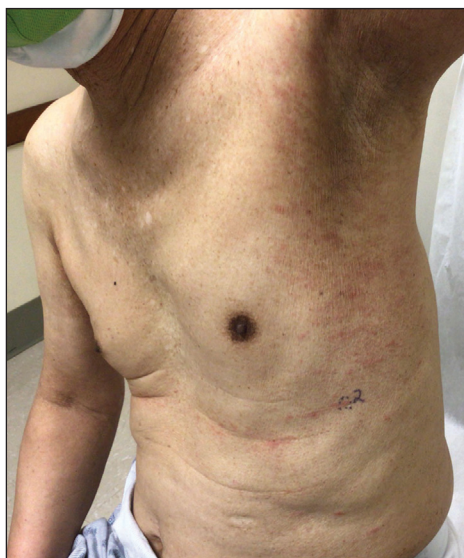


FIGURE 1. Multiple erythematous, hyperpigmented, pityriasiform papules and plaques within the axillae.

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The authors report no conflict of interest.

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biopsy from the left axilla demonstrated a mild lichenoid and perivascular lymphocytic infiltrate with scattered eosinophils, neutrophils, and extravasated erythrocytes. The overlying epidermis showed spongiosis with parakeratosis in addition to lymphocytic exocytosis (Figure 2). No fungal organisms were highlighted on periodic acid–Schiff staining. After this evaluation, we recommended that the patient discontinue lenalidomide and start taking a topical over-the-counter corticosteroid for 2 weeks. Over time, he noted marked improvement in the eruption and associated pruritus.

After a drug holiday of 2 months, the patient resumed a maintenance dosage of oral lenalidomide 10 mg/d. Four or 5 days after restarting lenalidomide, a pruritic eruption appeared that involved the axillae and the left lower abdomen, circling around to the left lower back. The axillary eruption resolved with a topical over-the-counter corticosteroid; the abdominal eruption persisted.

At the 3-month follow-up visit, physical examination revealed erythematous macules and papules that coalesced over a salmon-colored base along the lines of Blaschko extending from the left lower abdominal quadrant, crossing the left flank, and continuing to the left lower back without crossing the midline (Figure 3).

We recommended that the patient continue treatment through this eruption; he was instructed to apply a corticosteroid cream and resume lenalidomide at the maintenance dosage. A month later, he reported that the eruption and associated pruritus resolved with the corticosteroid cream and resumption of the maintenance dose of lenalidomide. The patient noted no further spread of the eruption.

Cutaneous adverse events are common following lenalidomide. In prior trials, the overall incidence of any-grade rash following lenalidomide exposure was 22% to 33%.⁵ A meta-analysis of 10 trials determined the overall

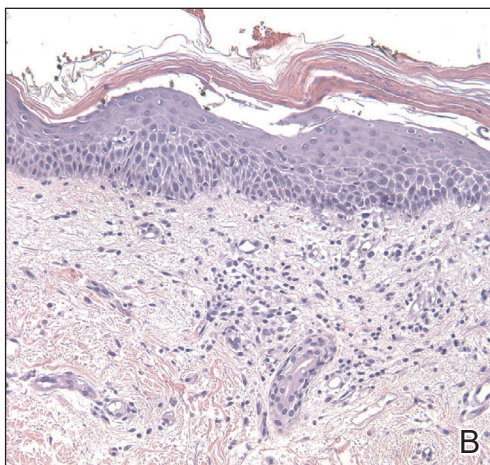
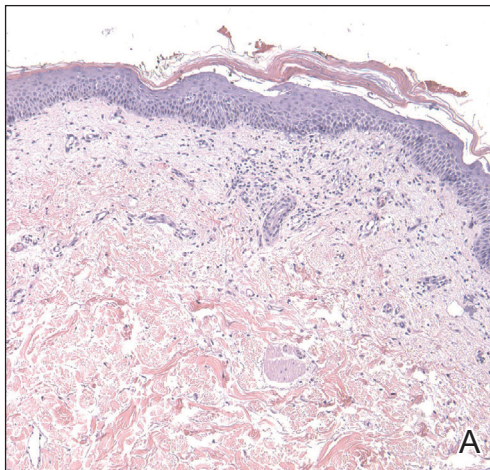


FIGURE 2. A and B, A biopsy specimen of the left axilla demonstrated a mild lichenoid and perivascular lymphocytic infiltrate containing scattered eosinophils, neutrophils, and a few extravasated erythrocytes. The overlying epidermis was spongiotic with parakeratosis and lymphocytic exocytosis (H&E, original magnifications $\times 100$ and $\times 200$).

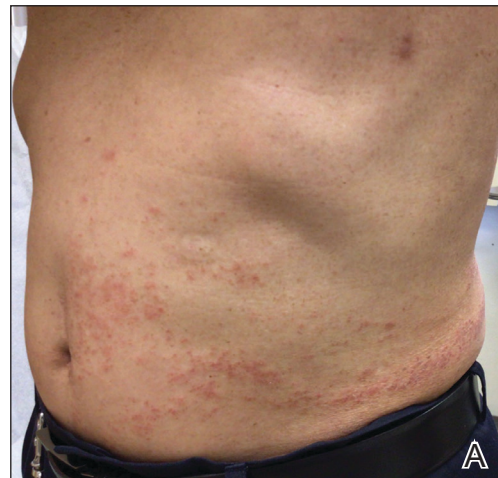


FIGURE 3. A and B, At a 3-month follow-up visit, erythematous macules and papules coalesced over a salmon-colored base along the lines of Blaschko extending from the left lower abdominal quadrant, crossing the left flank, and continuing to the left lower back without crossing the midline.

incidence of all-grade and high-grade cutaneous adverse events after exposure to lenalidomide was 27.2% and 3.6%, respectively.⁶ Our case represents a pityriasiform eruption due to lenalidomide followed by a secondary eruption suggestive of blaschkitis.

The rash due to lenalidomide has been described as morbilliform, urticarial, dermatitic, acneform, and undefined.⁷ Lenalidomide-induced rash typically develops during the first month of therapy, similar to our patient's presentation. It has even been observed in the first week of therapy.⁸ Severe reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported.^{5,6} Risk factors associated with rash secondary to lenalidomide include advanced age (≥ 70 years), presence of Bence-Jones protein-type MM in urine, and no prior chemotherapy.⁸ Our patient had 2 of these risk factors: advanced age and no prior chemotherapy for MM. The exact pathogenesis by which lenalidomide leads to a pityriasiform eruption, as in our patient, or to a rash in general is unclear. Studies have hypothesized that a lenalidomide-induced rash could be attributable to a delayed hypersensitivity type IV reaction or to a reaction related to the molecular mechanism of action of the drug.⁹

At the molecular level, the antimyeloma effects of lenalidomide include promoting degradation of transcription factors IKZF1 and IKZF3, which subsequently increases production of IL-2.^{1,2,9} Recombinant IL-2 has been associated with an increased incidence of rash in other cancers.⁹ Overexpression of programmed death 1 (PD-1) and its ligand (PD-L1) has been demonstrated in MM; lenalidomide has been shown to downregulate both PD-1 and PD-L1. Patients receiving PD-1 and PD-L1 inhibitors commonly have developed rash.⁹ However, the association between lenalidomide and its downregulation of PD-1 and PD-L1 leading to rash has not been fully elucidated. Given the multiple malignancies in our patient—MM, prostate cancer, malignant carcinoid tumor—an underlying paraneoplastic phenomenon may be possible. Additionally, because our patient initially received dexamethasone along with lenalidomide, the manifestation of the initial pityriasiform rash may have been less severe due to the steroid use. Although our patient underwent a 2-month drug holiday following the initial pityriasiform eruption, most lenalidomide-induced rashes do not necessitate discontinuation of the drug.^{5,7}

Our patient's secondary drug eruption was clinically suggestive of lenalidomide-induced blaschkitis. A report of a German patient with plasmacytoma described a unilateral papular exanthem that developed 4 months after lenalidomide was initiated.¹⁰ The papular exanthem following the lines of Blaschko lines extended from that patient's posterior left foot to the calf and on to the thigh and flank,¹⁰ which was more extensive than our patient's eruption. Blaschkitis in this patient resolved with a

corticosteroid cream and UV light therapy¹⁰; lenalidomide was not discontinued, similar to our patient.

The pathogenesis of our patient's secondary eruption that preferentially involved the lines of Blaschko is unclear. After the initial pityriasiform eruption, the secondary eruption was blaschkitis. Distinguishing dermatoses from the lines of Blaschko, which are thought to represent pathways of epidermal cell migration and proliferation during embryologic development, is important. Genodermatoses such as incontinentia pigmenti and hypomelanosis of Ito involve the lines of Blaschko¹¹; other disorders in the differential diagnosis of linear configurations include linear lichen planus, linear cutaneous lupus erythematosus, linear morphea, and lichen striatus.¹¹ Notably, drug-induced blaschkitis is rare.

Cutaneous adverse reactions from thalidomide analogues are relatively common. Our case of lenalidomide-associated blaschkitis that developed following an initial pityriasiform drug eruption in a patient with MM highlights that dermatologists need to collaborate with the oncologist regarding the severity of drug eruptions to determine if the patient should continue treatment through the cutaneous eruptions or discontinue a vital medication.

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