

Crizotinib-Induced Lichenoid Drug Eruption in a Patient With Lung Cancer

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PRACTICE POINTS

- Cutaneous lichenoid drug eruptions (LDEs) and photosensitive rash may be caused by crizotinib.
- The clinical morphology of LDE may resemble lichen planus, but certain features, such as larger skin lesions, the absence of Wickham striae, and photo-distribution, help to differentiate between the two.

Crizotinib was approved by the US Food and Drug Administration in 2011 for the treatment of anaplastic lymphoma kinase (ALK)- or ROS1-positive non-small cell lung cancer (NSCLC). Since then, the number of indicated uses for crizotinib has substantially increased. However, the administration of crizotinib can be associated with various adverse events. It is important that clinicians identify adverse cutaneous manifestations of crizotinib and are aware of their outcomes and treatments to avoid unnecessarily discontinuing a potentially life-saving medication. We describe a case of lichenoid drug eruption (LDE) that appeared 4 weeks after initiation of treatment with crizotinib in a 61-year-old man with ALK-positive metastatic lung adenocarcinoma.

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Crizotinib is a multitargeted tyrosine kinase inhibitor that blocks anaplastic lymphoma kinase (ALK), hepatocyte growth factor receptor (c-Met), and their oncogenic variants ALK fusion proteins or c-Met/hepatocyte growth factor receptor mutant variants.¹ Additionally, crizotinib was approved by the US Food and Drug Administration in 2011 for the treatment of patients with non-small cell lung cancer (NSCLC)

whose tumors are echinoderm microtubule-associated proteinlike 4 (EML4)/ALK or ROS1 positive.^{2,3} Among unselected populations of patients with NSCLC, the frequency of EML4/ALK rearrangements ranges from 1.5% to 6.7%.¹ Crizotinib is superior to standard chemotherapy in patients with ALK-positive NSCLC.²

In clinical trials, adverse reactions (grades 1 to 4) to crizotinib occurring in at least 25% of patients included visual disturbances, gastrointestinal tract disorders, fatigue, and pitting edema.^{1,2,4} Adverse reactions (grades 3 and 4) occurring in more than 5% of patients included elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels, dyspnea, pneumonia, and neutropenia.^{1,4} Although the incidence of dermatologic adverse reactions is approximately 11%, substantial progression of drug eruptions rarely has been reported.^{2,5} We describe a case of lichenoid drug eruption (LDE) that appeared 4 weeks after initiation of crizotinib treatment in a patient with ALK-positive metastatic lung adenocarcinoma.

Case Report

A 61-year-old man presented with a history of ALK-positive NSCLC with lung-to-lung metastasis and pleural seeding treated with a right lower lobectomy and chemotherapy 9 years prior. Chemotherapy was reattempted 5 years later. Targeted therapy with gefitinib was initiated following the lobectomy and 5 years later with erlotinib. The NSCLC was stable, as indicated by computed tomography performed once every 3 or 6 months. After 5 years of treatment, follow-up computed tomography showed slowly growing nodular shadows in the right middle and lower lung fields. Due to this disease progression, treatment with crizotinib (250 mg twice daily) was initiated. Four weeks after the initiation of crizotinib therapy, mild

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itchy skin eruptions developed on all extremities and the lower lip. He also reported that the skin lesions became more itchy and red with sun exposure. He had no history of drug allergies and denied taking any other medications.

Physical examination revealed multiple brown to violaceous, slightly scaly, flat-topped polygonal papules or plaques on both lower legs (Figure 1A), dorsal hands (Figure 1B), and extensor sites of the elbows, as well as lacelike fine white lines on the lower lip (Figure 1C). There were no nail lesions. The patient's dermatologic history was unremarkable, except for a few vitiligo lesions on the dorsal hands, extensor sites of the elbows, and mouth angles diagnosed 20 years earlier.

A skin biopsy from the right dorsal hand revealed a lichenoid infiltrate in the superficial dermis composed of lymphocytes, histiocytes and scattered eosinophils, focal parakeratosis, focal hypergranulosis, mild acanthosis, and basal vacuolization (Figure 2A). In addition, some dyskeratotic keratinocytes in the stratum spinosum and granulosum were identified (Figure 2B). The histopathology was consistent with the diagnosis of an LDE. Direct immunofluorescence revealed no globular or cytooid body-like deposits of immunoglobulin, with IgM, IgA, IgG, or C3 in the epidermis, dermis, and basement membrane zone. Routine laboratory studies revealed elevated liver enzymes, including an ALT level of 115 U/L (reference range, 0–40 U/L) and AST level of 60 U/L (reference range, 5–45 U/L). Negative results for the serum hepatitis B surface antigen and anti-hepatitis C virus tests were recorded. The patient had no medical history of alcohol consumption or abnormal liver function tests. The skin lesions were treated with diflucortolone valerate fatty ointment 0.1% twice daily and abnormal liver functions were treated with silymarin (150 mg per cap twice daily). He experienced some improvement.

A causality assessment was performed using the Naranjo Adverse Drug Reaction Probability Scale,^{6,7} and we concluded that crizotinib was the possible cause (Naranjo score, 4) of this adverse drug reaction (Table). Because the skin reaction was tolerable and liver enzymes were mildly elevated (ALT, 50 U/L; AST, 48 U/L), the offending drug was continued to benefit the underlying disease. His NSCLC was stable on computed tomography 3 months later.

Comment

The number of indicated uses of crizotinib, an oral small-molecule ALK tyrosine kinase inhibitor for the treatment of NSCLC, has gradually increased, but only a few cases of cutaneous adverse reactions, such as erythema multiforme and severe photosensitivity dermatitis, have been reported.^{2,5} Skin toxicity is a common and well-known side effect of other small-molecule tyrosine kinase inhibitors, particularly epidermal growth factor receptor inhibitors.⁸ However, LDE is not commonly associated with small-molecule tyrosine kinase inhibitors, though it has been described in a few patients taking imatinib for



FIGURE 1. Multiple ill-defined, brown to violaceous, slightly scaly, flat-topped polygonal papules or plaques on the left lower leg (A) and right dorsal hand (B) as well as lacelike fine white lines on the lower lip (C).

chronic myelogenous leukemia and gastrointestinal tract stromal tumors.^{9,10}

The clinical morphology of LDE may resemble lichen planus, but certain features, such as larger skin lesions, the absence of Wickham striae, and photodistribution, help to differentiate between the two.¹⁰ Histologically, some findings are more common in LDE, including focal parakeratosis, cytooid bodies in the cornified and granular layers, and the presence of eosinophils.¹¹

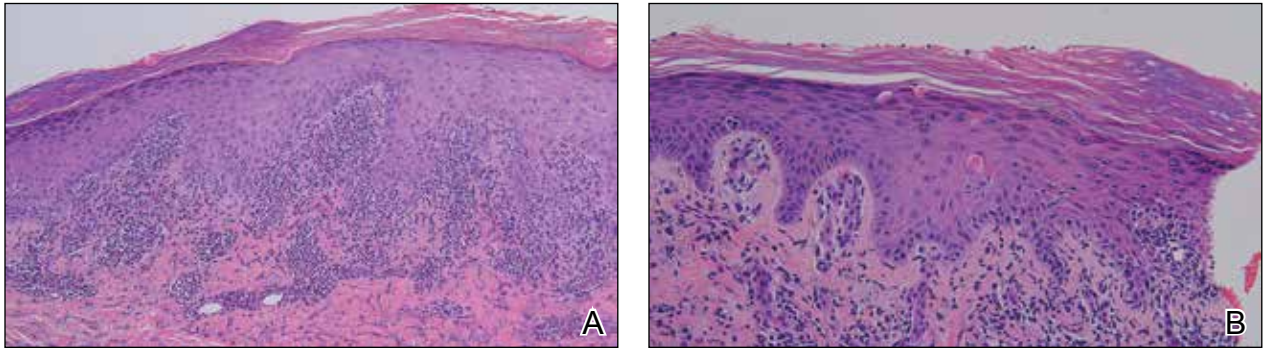


FIGURE 2. Histopathology showed a lichenoid infiltrate in the superficial dermis composed of lymphocytes, histiocytes and scattered eosinophils, focal parakeratosis, focal hypergranulosis, mild acanthosis, and basal vacuolization (A)(H&E, original magnification $\times 100$). Some dyskeratotic keratinocytes were identified in the stratum spinosum and granulosum (B)(H&E, original magnification $\times 200$).

The Naranjo Adverse Drug Reaction Probability Scale and Score for a Patient With Crizotinib-Induced Lichenoid Drug Eruption

Question	Score ^a			
	Yes	No	Do Not Know	Our Patient's Score ^b
1. Are there previous <i>conclusive</i> reports on this reaction?	+1	0	0	0 (no)
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0	+2 (yes)
3. Did the adverse reaction improve when the drug was discontinued or a <i>specific</i> antagonist was administered?	+1	0	0	0 (do not know)
4. Did the adverse event reappear when the drug was readministered?	+2	-1	0	0 (do not know)
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	+2 (no)
6. Did the reaction reappear when a placebo was given?	-1	+1	0	0 (do not know)
7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	0 (do not know)
8. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0	0 (do not know)
9. Did the patient have a similar reaction to the same or similar drugs in <i>any</i> previous exposure?	+1	0	0	0 (no)
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	0 (no)

^aNaranjo Adverse Drug Reaction Probability Scale: ≥ 9 =definite adverse drug reaction; 5–8=probable adverse drug reaction; 1–4=possible adverse drug reaction; 0=doubtful adverse drug reaction.

^bOur patient's total score was 4 (possible adverse drug reaction).

Adapted from Naranjo et al.⁶

Our patient developed lichenoid rashes after 1 month of crizotinib therapy. The latency period for developing a medication-induced LDE varies from months to 1 year and is dependent on the dosage, host response, prior exposure, and concomitant drug administration. No additional medications had been added to our

patient's regimen after initiating crizotinib therapy, and he did not take any other known medications. Ultimately, based on the time-event relationship, morphology, distribution, and histopathologic findings, we concluded that our patient developed an LDE due to crizotinib.

Our patient also had a history of vitiligo affecting the hands, elbows, and mouth angles for 20 years. Although there are limited reports of a possible causal link between lichen planus or drug-induced lichen planus eruption and vitiligo,¹²⁻¹⁴ we do not think these conditions were associated in our case because the patient's vitiligo lesions persisted for many years, did not progress, and remained inactive and stable, and there was a lack of colocalization of LDE and vitiligo.

Our patient reported that the skin eruptions worsened after sun exposure. Oser and Janne⁵ also reported a patient with ALK-positive metastatic lung adenocarcinoma who developed severe crizotinib-induced photosensitive rashes. Further accumulation of similar cases and pathophysiological studies will be necessary to clarify whether this photosensitivity dermatitis is caused by ALK inhibition itself or mediated through host-immune mechanisms.⁵

Conclusion

As crizotinib prescriptions for patients with NSCLC are increasing, clinicians should be aware of the possibility of cutaneous LDEs occurring as an adverse effect. Additionally, physicians should treat appropriately to avoid unnecessarily discontinuing a potentially life-saving medication and to improve quality of life for patients with NSCLC who are treated with crizotinib.

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