CASE REPORT

Osimertinib-Induced Cutaneous Vasculitis Responsive to Low-Dose Dapsone Without Interruption of Anticancer Therapy: A Case Report and Review of the Literature

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ABSTRACT

A 45-year-old woman with a history of lung adenocarcinoma treated with osimertinib developed purpuric plaques and vesicles on the lower extremities after 5 months of therapy. Skin biopsy revealed leukocytoclastic vasculitis (LCV). A workup for systemic involvement was unremarkable. The patient was treated with oral dapsone while continuing osimertinib without interruption. Skin lesions cleared within 2 weeks of therapy with no recurrence after titrating off dapsone. To the best of our knowledge, this is the first reported case of LCV induced by a small-molecule EGFR inhibitor in which therapy was not interrupted. This is also the first reported case treated with dapsone rather than systemic corticosteroids. We suggest consideration of dapsone to treat skin-limited LCV induced by EGFR inhibitors in patients with lung cancer without features of systemic vasculitis. In addition, this case highlights that it may not be necessary to stop EGFR inhibitor therapy in the absence of severe features such as ulceration, bullae, necrosis, or severe pain. Dapsone is an effective targeted therapy for cutaneous LCV that does not globally impair the immune system and may allow for uninterrupted treatment of the underlying malignancy.

Keywords: Cutaneous vasculitis; Osimertinib; Epidermal growth factor receptor inhibitor; Case report; Dapsone

Introduction

Osimertinib is a small molecule inhibitor of the intracellular tyrosine kinase domain of the EGFR. It is approved for the treatment of specific EGFR-mutated NSCLC. Skin toxicities attributed to EGFR inhibitors include acneiform and papulopustular dermatitis, xerosis, pruritus, and paronychia (though their incidence with osimertinib is less than inhibitors that more readily bind wild-type EGFR in the skin).[1]

Emerging reports of purpura and cutaneous vasculitis from EGFR inhibitors have risen over the past several years.[2–4] At least a dozen cases have been published since 2007 (eight in patients with lung cancer). In all cases treated for NSCLC, therapy with EGFR inhibitor was interrupted despite vasculitis being limited to the skin (Table 1).

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Table 1. Summary of Published Cases of Small-Molecule EGFR Inhibitors Inducing Cutaneous Vasculitis in Patients With Lung Cancer

Manuscript	EGFR Inhibitor	Onset of LCV After Therapy Initiation	Biopsy Proven?	EGFR Inhibitor Therapy Interrupted?	Treatment	Outcome of Rechallenge
Uchimiya et al. (2010)[3]	Geftinib	1 mo	Yes	Yes	None	No recurrence at same dose
Uchimiya et al. (2010)[3]	Geftinib	2 mo	Yes	Yes	None	No recurrence at same dose
Ko et al. (2011)[6]	Geftinib	4 mo	Yes	Yes	Prednisolone (20 mg daily; end date not reported)	Recurrence
Fekete and Fekete. (2019)[4]	Erlotinib	8 mo	Yes	Yes	Prednisolone (1 mg/kg for 2 wk tapered over 7 wk)	No recurrence at reduced dose
Su et al. (2012)[7]	Erlotinib	6 wk	Yes	Yes	None	No recurrence at reduced dose
Boeck et al. (2016)[8]	Erlotinib	80 d	Yes	Yes	None	No recurrence at reduced dose
Rungtrakulchai et al. (2014)[9]	Erlotinib	3 d	Yes	Yes	None	Recurrence at reduced dose
Hamada et al. (2019)[2]	Osimertinib	6 wk	Yes	Yes	Prednisolone (25 mg daily; end date not reported)	No recurrence at same dose (with prednisolone prophylaxis)
Our patient	Osimertinib	5 mo	Yes	No	Dapsone (50 mg daily for 2 wk tapered over 4 wk)	Clearance without recurrence

LCV, leukocytoclastic vasculitis.

We report a case of leukocytoclastic vasculitis (LCV) induced by osimertinib in a patient with lung adenocarcinoma who was treated with dapsone after ruling out systemic disease. Therapy with osimertinib was not interrupted and the patient experienced clearance of LCV despite continued therapy with osimertinib. Our case is the first in the literature without interruption in EGFR inhibitor therapy, and the first case treated

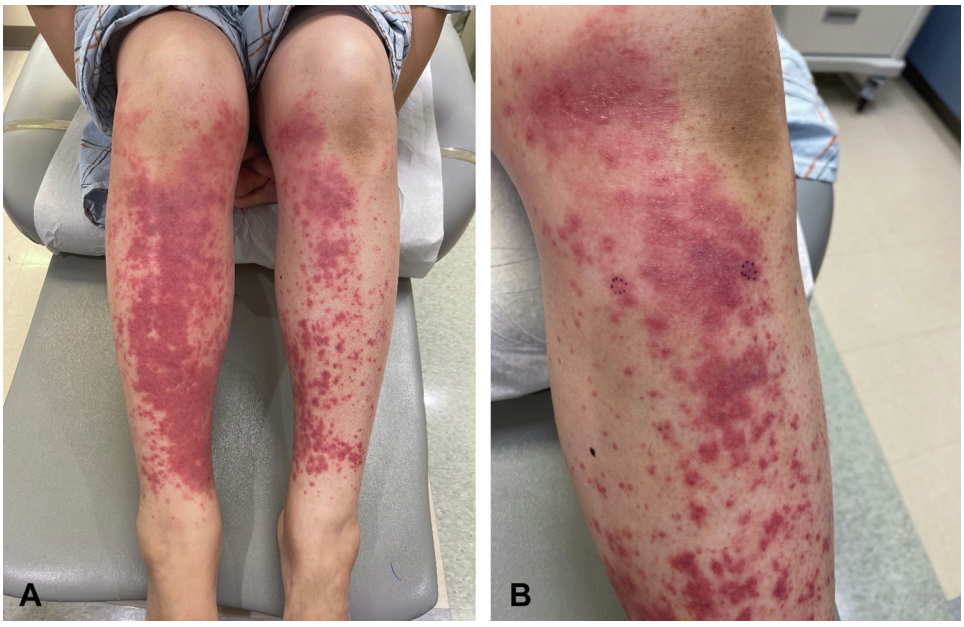

Figure 1. Panel *A* illustrates palpable purpura over the bilateral lower extremities, extending from the ankles to the inferior knees bilaterally. Panel *B* also reveals vesicles just inferior and medial to the right knee.

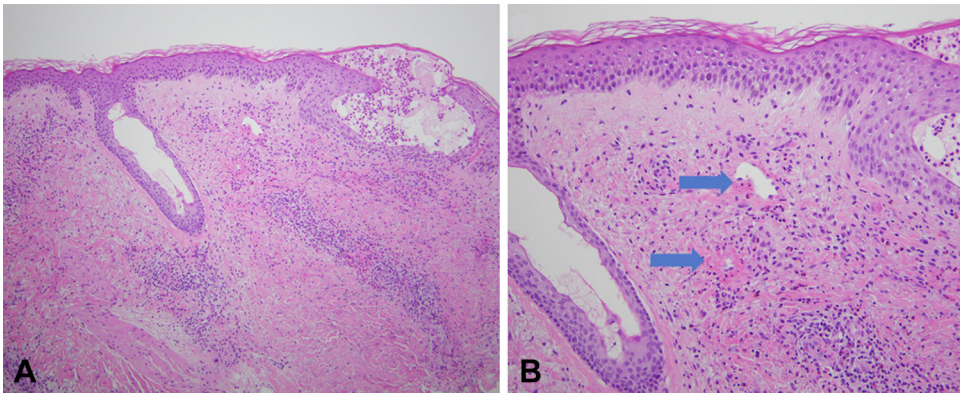

Figure 2. Leukocytoclastic vasculitis. Panels *A* and *B* reveal spongiosis and mixed neutrophilic and eosinophilic perivascular inflammation (10× and 20× magnification, respectively). Fibrin deposition and extravasation involving superficial dermal vessel walls with endothelial cell enlargement are present (arrows), consistent with fibrinoid necrosis. All had hematoxylin and eosin staining.

without systemic corticosteroids. We hope reporting this case will encourage providers to consider dapsone to treat skin-limited LCV induced by EGFR inhibitors. In addition, we note that discontinuation or interruption of the EGFR inhibitor may not be necessary in the absence of systemic vasculitis or severe features.

Case Presentation

A 45-year-old woman with no past medical history presented with dyspnea on exertion and was found to have a right lower lobe pulmonary embolus. Computed tomography of the chest revealed a 2.5 by 1.5 by 2.3 centimeter left lower lobe lung mass with ipsilateral hilar, axillary, and mediastinal lymphadenopathy. The patient was started on rivaroxaban and underwent a lung biopsy.

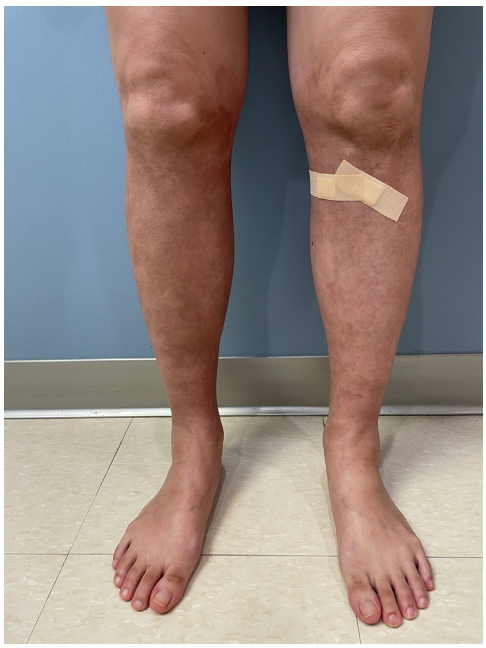

Figure 3. Clearance of cutaneous vasculitis after 2 weeks of dapsone therapy at 50 mg daily.

Biopsy of the mass revealed lung adenocarcinoma. Molecular testing revealed an exon-19 EGFR deletion mutation. Positron emission tomography–computed tomography revealed diffuse bone metastases. The patient was started on monotherapy with osimertinib 80 mg daily.

Five months into therapy, the patient noted a rash that started at her ankles bilaterally and expanded in size. She was evaluated and diagnosed with traumatic petechiae likely from compression stocking use. Over the next several months, the rash continued to progress and became pruritic and at times painful. She then developed small vesicles over the original papules and was referred to dermatology.

On examination, the patient had nonblanching petechiae and coalescent purpura over the bilateral lower extremities from the knees to the ankles, with overlying vesicles (Fig. 1*A* and *B*). The patient was otherwise feeling well and denied fevers, chills, arthralgias, hematuria, abdominal pain, or other symptoms. Her only medications included rivaroxaban, calcium-vitamin D, and an oral contraceptive— the latter two of which, she had been on for years. She did not take any supplements or over-the-counter medications.

Renal and liver function and complete blood count (CBC) were unremarkable. Serum immunoglobulin A and glucose-6-phosphate dehydrogenase levels were normal. Urinalysis was negative for hematuria or proteinuria. Skin punch biopsies were obtained for histopathology and direct immunofluorescence. Pathology results revealed florid dermal chronic inflammation and eosinophils with dermal hemorrhage and focal vasculopathic changes with fibrinoid necrosis of vessel walls (Fig. 2*A* and *B*). Direct immunofluorescence revealed focal 1+ IgA and complement 3 deposition in the papillary dermal

vessels walls. A diagnosis of drug-induced LCV was made.

Given the absence of other inciting factors, osimertinib was felt to be the trigger. A multidisciplinary decision was made between oncology and dermatology to continue EGFR inhibitor therapy and initiate dapsone 50 mg daily. Within 2 weeks of treatment, her skin lesions entirely resolved (Fig. 3). Her dapsone dose was gradually reduced over the next 6 weeks without recurrence of LCV. She then came off dapsone therapy and has not had recurrence of LCV for over 10 months. She has continued osimertinib without interruption.

Discussion

LCV is an emerging toxicity of EGFR inhibitors, which may have a direct effect on capillaries owing to EGFR expression on endothelial cells of cutaneous blood vessels, suggesting a possible mechanism for inducing vasculitis.[3,5]

Cutaneous adverse events are a frequent cause of therapy interruption, dose reduction, or discontinuation in patients with malignancy. In Table 1, we summarize all reported cases in which small-molecule EGFR inhibitors caused LCV in patients with lung cancer (with our case included). The onset of LCV has occurred anywhere from 3 days to 8 months after therapy initiation. In all but one case, LCV onset occurred at least 2 months after therapy initiation, suggesting that it is typically a delayed toxicity. The lower extremities were the most involved location. All cases were limited to the skin with no systemic disease.

Previous studies have suggested the use of systemic corticosteroids when the EGFR inhibitor is continued.[2] We suggest considering the use of dapsone in patients without features of systemic vasculitis or contraindications to dapsone therapy, as this is a more specific treatment for LCV (by means of neutrophil inhibition). A baseline glucose-6-phosphate dehydrogenase screen, CBC, and liver function test should be obtained before treatment; CBC and transaminases should be monitored every 2 to 4 weeks for the first 2 months of therapy and then every 3 to 4 months thereafter. Patients should be counseled on possible adverse effects including hemolytic anemia, methemoglobinemia, neuropathy, neutropenia, agranulocytosis, hepatotoxicity, and hypersensitivity reactions.

For patients with LCV limited to the skin, it may not be necessary to stop EGFR inhibitor therapy in the absence of severe features such as ulceration, bullae, necrosis, or severe pain. Concomitant toxicity and malignancy-directed therapy can be considered. Multidisciplinary discussions assessing the individualized risk of cancer progression versus toxicity progression and the ability to monitor for both are vital. To our knowledge, this case is the first in the literature treated with dapsone and the only case in which EGFR inhibitor therapy was not interrupted and in which systemic steroids were avoided. Dapsone is a targeted agent for LCV that is not globally immune-suppressing and has fewer adverse effects than long-term systemic steroid use. Dapsone may also allow for uninterrupted treatment of the patient's malignancy.

CRediT Authorship Contribution Statement

Christopher Iriarte: Conceptualization, Data curation, Visualization, Writing-original draft, Writing-review & editing.

Jonathan H. Young: Visualization, Writing-review & editing.

Michael S. Rabin: Supervision, Writing-review & editing.

Nicole R. LeBoeuf: Conceptualization, Supervision, Visualization, Writing-review & editing.

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Informed consent was obtained from patient in writing.

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