Case Report

Crizotinib-induced Photoallergic Dermatitis: A Case Report of an Unconventional Adverse Effect of a Novel Molecule

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Abstract

Crizotinib is a novel tyrosine kinase inhibitor approved globally for the treatment of patients with locally advanced or metastatic non-small cell lung carcinoma (NSCLC) which is anaplastic lymphoma kinase (ALK) positive. It is an ATP-competitive small-molecule inhibitor of the receptor tyrosine kinases, namely, c-Met, ALK, and ROS 1. Cutaneous toxicity is encountered in >50% of patients on tyrosine kinase inhibitors and they include acne-like (acneiform) rash, discoloration, dryness, and hyperkeratosis of the skin, perifollicular inflammation, acral erythema, panniculitis, paronychia, periungual splinter hemorrhages, alopecia, facial hypertrichosis, and changes in the structure of the eyelashes, hair, and nails. Crizotinib frequently results in gastrointestinal disturbances, visual impairment, peripheral edema, QT-prolongation, and liver enzyme elevation. Photoallergic dermatitis with crizotinib is rare. We hereby report a case of a 50-year-old male with ROS 1 positive metastatic adenocarcinoma of the lung on crizotinib who presented with multiple well- to ill-defined erythematous plaques over both photo exposed and covered sites involving the face, neck, chest, shoulder, forearms, and dorsum of both hands. Based on the history, temporal association with the intake of the drug and histopathological evidence, a diagnosis of photo-allergic dermatitis was made. Lesions regressed in 4 weeks with the use of oral and topical steroids, emollients, and strict photoprotection. Regular, prophylactic, photoprotective measures in patients on photosensitizing drugs like crizotinib reduces the overall morbidity and improves their quality of life.

Keywords: Crizotinib, nonsmall cell lung cancer, photoallergic dermatitis, receptor tyrosine kinase inhibitor

Introduction

Adverse drug reactions are frequent and account for 3.5% of all hospital admissions.[1] They have varied presentations ranging from innocuous exanthematous eruptions to serious, life-threatening reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis. Drug-induced photosensitivity is frequently encountered and represent 8% of cutaneous adverse drug reactions.[2] Till date, more than 300 drugs have been documented to induce photosensitivity.[3] Several newer drugs are being added to this list with the rapid advances in medical science.

Crizotinib is approved by the US food and drug administration for the treatment of nonsmall cell lung carcinoma (NSCLC).[4] Crizotinib-induced photosensitive dermatitis is extremely rare. In the existing literature, a case of phototoxic dermatitis due to this drug has been described, and to the best of our knowledge, this is the first case of crizotinib-induced photo-allergic dermatitis to be reported.[5]

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Case Report

A 50-year-old male with ROS 1 positive adenocarcinoma lung (Stage IV) on tablet crizotinib 250 mg for 5 months was referred from the Department of Oncology with the complaints of multiple red raised lesions associated with itching on the face, neck, chest, and upper extremities since 2 days following a bout of sun exposure. He gave history of many such milder episodes in the past 4 months and aggravation of the lesions on sun-exposure. There was no history of oral ulcers, joint pains, use of dyes, or any other photosensitizing drugs. He had no history of any drug allergies in the past. On dermatologic

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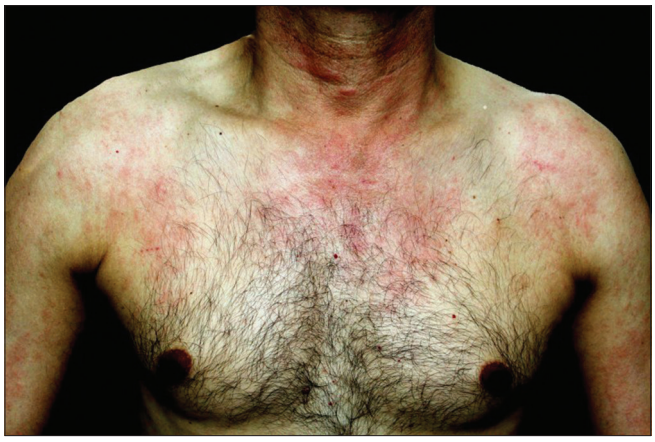

Figure 1: Multiple erythematous plaques seen over photoexposed "V" area of the neck and photoprotected shoulders and arms

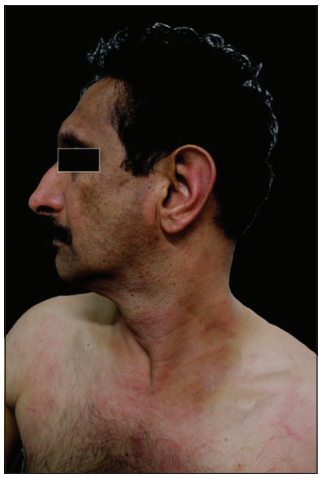

Figure 2: Ill-defined erythematous plaques seen over the face, pinna of ear, neck, and upper chest

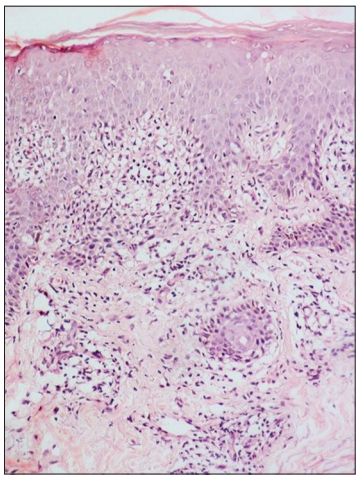

Figure 3: Epidermis showing marked spongiosis, vacuolar interface changes, lymphocytic exocytosis, and dense perivascular monocytic infiltrate seen in papillary dermis (H and E, ×100)

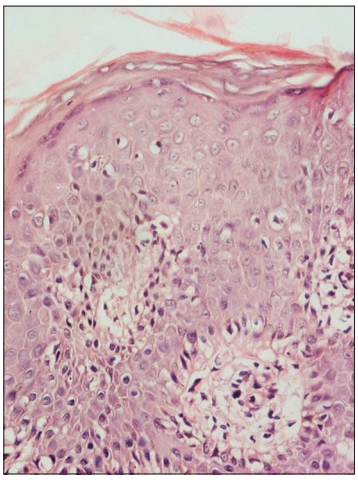

Figure 4: Marked spongiosis with lymphocytic exocytosis seen in epidermis (H and E, ×400)

examination, multiple well- to ill-defined erythematous plaques were observed over both photo exposed and covered sites involving the face, neck, chest, shoulders, forearms, and dorsum of both hands [Figures 1 and 2]. Mucosa and appendages of the skin were unremarkable.

Considering the risk-benefit ratio, crizotinib was continued, and the photo-patch test could not be done. His hematological and biochemical investigations were within normal limits.

Histopathology of the skin showed orthokeratosis, parakeratosis, spongiosis, focal acanthosis, vacuolar interface changes, and lymphocytic exocytosis in the epidermis. Papillary dermis showed marked edema with dense perivascular monocytic infiltrate with occasional neutrophils and plasma cells [Figures 3 and 4]. A diagnosis of crizotinib-induced photoallergic dermatitis was arrived at based on the history, temporal association with the intake of the drug, distribution of lesions over both sun-exposed and covered sites and the histopathological findings. The patient was advised strict photoprotection and treated with a short course of systemic corticosteroids along with topical steroids, emollients, and oral anti-histamines. Lesions subsided over a period of 4 weeks, and the patient continues to be on photo-protective measures.

Discussion

Lung cancer is one of the leading causes of cancer-related mortality in the community. Nonsmall cell lung carcinoma (NSCLC), a subtype of lung carcinoma accounts for 85% of all the cases.[6] In recent years, there has been a major paradigm shift in its management of nonsmall cell lung cancer. Targeted therapy is the current standard of care for the treatment of NSCLC with detectable mutations and significantly improves the patient outcome.

Crizotinib is an inhibitor of the receptor tyrosine kinases, namely, c-Met (C-mesenchymal epithelial transition factor oncogene kinase), anaplastic lymphoma kinase, and proto-oncogene tyrosine-protein kinase ROS 1. Most common systemic adverse effects noted with crizotinib include nausea, diarrhea, vomiting, visual impairment, fatigue, edema,

lymphopenia, and transaminitis. Nonspecific skin rashes were noted in about 10% of patients in phase I and III clinical trials.[7] Photosensitive dermatitis induced by this drug is extremely rare, and the first case has been reported by Oser and Jänne in 2014. They reported phototoxic dermatitis with areas of exfoliation limited to sun-exposed areas in a 71-year-old male with adenocarcinoma lung on crizotinib.[5]

Drug-induced photosensitivity occurs when the body is exposed to a drug or its metabolites and then subjected to either ultraviolet and/or visible light. Pathophysiology of development of photosensitivity involves direct damage to cell membranes and DNA in phototoxic reactions and cell-mediated immune response in Photoallergic reactions. The clinical distinction between the two types may be difficult. Phototoxic reactions have an early onset and are clinically well demarcated with erythema, edema, blistering and desquamation confined to sun-exposed sites. Photoallergic reactions require prior sensitization and manifest as eczematous dermatitis that may spread beyond the sun-exposed sites.[8]

Our patient had a temporal association of the development of photosensitive rash following the intake of crizotinib, eczematous plaques beyond the sun-exposed sites, and histopathological changes consistent with photo-allergic dermatitis. Identification and withdrawal of the culprit drug may be required in case of severe reactions. However, simple prophylactic sun protective measures like use of clothing with sleeves rolled down, avoiding sun exposure during peak hours, and use of sunscreens usually suffice in mild-to-moderate reactions.

Conclusion

With the increasing use of crizotinib by oncologists in the management of NSCLC, it is imperative for us to know the relevant cutaneous adverse effects of the molecule to help reduce patients' morbidity and improve their quality of life.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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