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Case Report

Dermatoses induced by multikinase inhibitors: A case report

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ABSTRACT

Multikinase inhibitors, such as sorafenib and lenvatinib, are used in the treatment of patients with renal and hepatocellular carcinoma. Their mechanism of action includes the inhibition of neoangiogenesis through VEGFR, KIT, PDGF, RET, and fibroblast growth factor receptors. A sixty-year-old patient of Indian origin presented to our dermatology OPD with a history of HCC under treatment with sorafenib and a twelve-month history of progressive, pruritic, erythematous, papulosquamous rash on the lower extremities, lumbosacral region, anterior abdomen, perianal region, and perineum. On examination, the patient had tender, desquamative lesions on the palms and soles. He had developed a bullous eruption on the lateral side of both feet and the dorsum of the ankle joint and foot. He was under treatment with sorafenib for twelve months and switched to lenvatinib for two months. ADRs require early diagnosis and effective management in order to make sure that lifesaving anti-neoplastic therapy may be continued uninterrupted.

Key words: Lenvatinib; Sorafenib; Multikinase inhibitors; HCC; Cutaneous reactions

INTRODUCTION

Multikinase inhibitors (MKIs), such as sorafenib and lenvatinib, are a group of drugs used in the treatment of patients with renal carcinoma and hepatocellular carcinoma. The main mechanism of action includes the inhibition of neoangiogenesis through VEGFR, KIT, platelet-derived growth factor receptors (PDGF), RET, and fibroblast growth factor receptors.

CASE REPORT

A sixty-year-old male of Indian origin presented to our outpatient dermatology department at a tertiary care center with a history of liver cirrhosis and HCC under treatment with sorafenib, with a twelve-month history of progressive, pruritic, erythematous, papulosquamous rash on the lower extremities and lumbosacral region and on the anterior abdomen, perianal region, and perineum. On examination, the patient had a tender, desquamative eruption on the palms and soles. He had developed a bullous eruption on the lateral side of both feet and the dorsum of the ankle joint and foot. He had undergone partial hepatectomy and cholecystectomy under treatment with sorafenib for twelve months and switched to lenvatinib two months previously.

A detailed cutaneous examination revealed a bullous eruption on the dorsum of the foot and the posterior and lateral aspects of the calcaneum, which were consistent with hand–foot–skin reaction (HFSR) (Figs. 1a and 1b). He also had tender, eczematous and erythematous plaques on the flexor aspect of the phalangeal joints on the bilateral palms (Fig. 2a). He developed multiple, lichenified plaques and callosities on the dorsal aspect of both feet and the posterior aspect of the calcaneal region, along with numerous pruritic, psoriasiform plaques on the thighs (Fig. 2b) and on the dorsum of the hand and phalanges (Fig. 2c). The patient had multiple, senile comedones on the zygomatic area and seborrheic keratosis and acneiform eruptions on the face. He also had erythematous papules on the

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forehead (Fig. 3a). A genital examination revealed an erythematous, pruritic eruption on the bilateral crural region, perineum, and perianal region (Fig. 3b). The patient had multiple, eruptive, cherry hemangioma on the anterior and posterior aspects of the chest and abdomen. He also had a bullous eruption on the lateral and posterior aspects of the bilateral foot, dorsum of the ankle joint, and dorsum of the foot.

A skin biopsy was taken from the lower limb and the microscopic picture showed vacuolar degeneration of basal cell keratinocytes with spongiosis, consistent with the features of lichenoid dermatitis. The patient was treated with a mild oral steroid, topical antibiotic, and potent corticosteroid, with moderate relief from the symptoms. The patient was switched to lenvatinib 4 mg BD for three months and had a recurrence of similar symptoms.

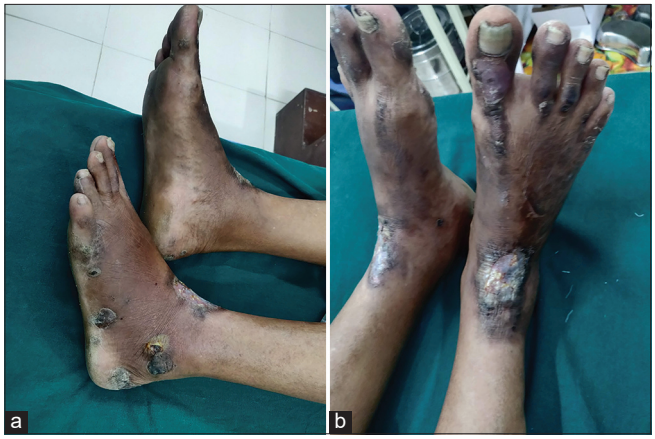

Figure 1: (a) Bullous eruption on the dorsum of the foot and the posterior and lateral aspects of the calcaneum, which were consistent with hand–foot–skin reaction (HFSR). (b) HFSR, healed bullous lesions with an eczematous surface on the dorsal aspect of the ankle and foot.

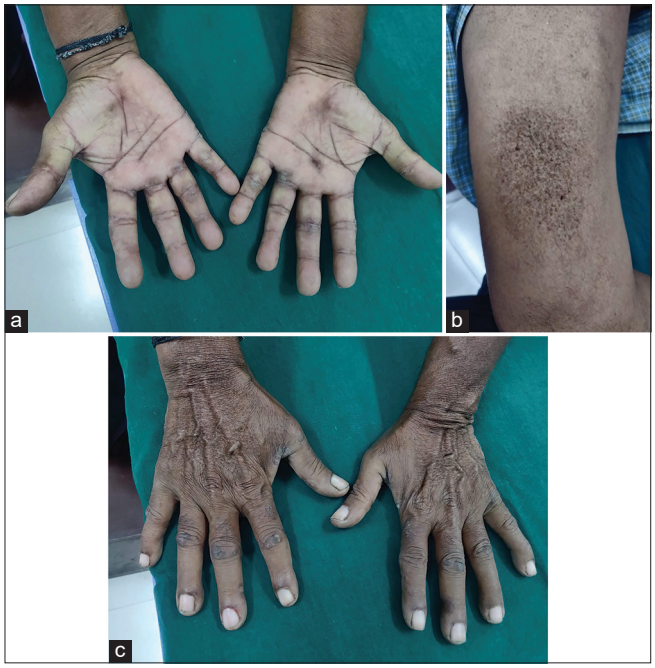

Figure 2: (a) Erythematous plaques on the flexor aspect of the phalangeal joints of the bilateral palms. (b) Pruritic psoriasiform plaques on the thighs. (c) Psoriasiform plaques on the dorsum of the hand and phalanges.

DISCUSSION

Sorafenib and lenvatinib are two related multikinase inhibitors (MKIs), which act by inhibiting VEGFR-1,2,3, PDGFR-β, RET, and KIT. The VEGF signaling pathway is the key pathway of the vasculature of different tumors, which helps in mediating endothelial cell proliferation, vascular permeability, vasodilation, and tumor migration and neovascularization [1].

Lenvatinib is an FDA-approved MKI for the treatment of various tumors, such as advanced HCC, advanced RCC, advanced endometrial carcinoma, and differentiated thyroid carcinoma. There are multiple side effects, both systemic and cutaneous, among which the most common are HFSR, psoriasiform eruption, palmoplantar dysesthesia, generalized xerosis, and papulosquamous rash [2]. The facial rash due to sorafenib is similar to seborrheic dermatitis associated with acneiform eruptions [3].

Clinically, hand–foot–skin reaction presents in the form of bullous rash or eczematous reaction predominantly on the sun-exposed areas of the body such as the acral region. The lesions may adversely affect the life of the patient, which may be measured by the Dermatology Life Quality Index (DQLI).

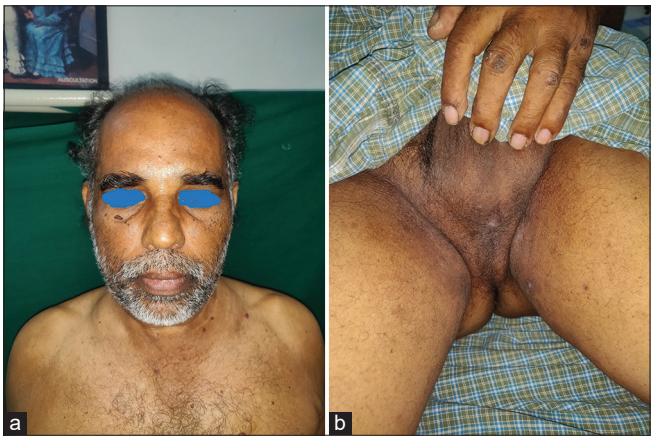

Figure 3: (a) Erythematous papules on the forehead with senile comedones. (b) Erythematous pruritic eruption on the bilateral crural region, perineum, and perianal region.

Hand–foot–skin reaction is also known to be acral site erythema or palmar and plantar erythro-dysesthesia and may present with other antineoplastic agents, including cytarabine, doxorubicin, capecitabine, and 5-fluorouracil. The incidence ranges from 7% to 70% depending on the type of the agent used [4]. Some of the cutaneous manifestations include abnormal paresthesia, pain or tenderness, exfoliation, eczematous reaction, and ill-defined inflammatory infiltrates in histopathology along with the features of lichenoid dermatitis. However, sorafenib-induced HFSR is most commonly associated with palmar or plantar hyperkeratosis [5].

The treatment of HFSR includes moisturizers, topical steroids, topical immunomodulators (TIMS), and keratolytic agents such as urea, lactic acid, and salicylic acid. It is recommended that patients with severe HFSR have their sorafenib dose adjusted, without discontinuation in the treatment protocol. Patients with cutaneous reactions manifesting immediately or within the first 2–4 weeks of initiating multikinase inhibitor therapy are particularly in need of prompt management to alleviate symptoms in order to improve the quality of life and to prevent progression to higher-grade HFSR [6].

VEGF has been implicated in the pathophysiology of psoriasis as it is overexpressed on psoriatic keratinocytes. This contributes to the hyperplasia of the epidermis and induces neoangiogenesis [7]. Therefore, it appears paradoxical that psoriasiform eruptions have been observed following sorafenib and even in lenvatinib therapy, given that both block VEGFR-1,2,3 signaling. On contrary, reports describe that treatment with sorafenib and sunitinib causes the remission of existing chronic plaque psoriasis.

Hypotheses for sorafenib-induced psoriasiform reactions include the hypoxia-inducible factor pathway, which is an upstream of the VEGF pathway. Sorafenib upregulates HIF-2α, which was found to be overexpressed in psoriasiform lesions [8]. Mechanisms by which VEGFR inhibitors such as lenvatinib induce or exacerbate psoriasis or psoriasiform eruptions are yet to be determined and may differ between MKIs due to the diversity in their target action and affinities with different immunomodulatory effects [9].

Other cutaneous effects, such as palmoplantar hyperkeratosis, keratosis pilaris-like eruption, multiple cysts, eruptive keratoacanthomas, and squamous cell carcinoma, have also been described in patients under treatment with sorafenib, which supports the hypothesis that sorafenib alters keratinocyte proliferation, differentiation, and neoangiogenesis [10].

CONCLUSION

Multikinase inhibitors, including sorafenib, may induce a variety of dermatologic adverse reactions. These ADRs require early diagnosis and effective management in order to make sure that lifesaving anti-neoplastic therapy may be continued uninterrupted. Observations as in this case may contribute to a better understanding of the side effects and aid physicians in the early management of the patients.

Consent

The examination of the patient was conducted according to the principles of the Declaration of Helsinki.

The authors certify that they have obtained all appropriate patient consent forms, in which the patients gave their consent for images and other clinical information to be included in the journal. The patients understand that their names and initials will not be published and due effort will be made to conceal their identity, but that anonymity cannot be guaranteed.

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