Sorafenib Induced Hand-Foot Skin Reaction at Low Dose

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Sir,

Sorafenib, a small multikinase inhibitor, is the Food and Drug Administration (FDA) approved for the treatment of advanced hepatocellular carcinoma and second-line treatment of primary renal cell carcinoma (RCC). Out of the various cutaneous side effects known to it, hand-foot skin reaction (HFSR) is one of the commonest cutaneous toxicity. We report a case of HFSR in a patient of RCC treated with sorafenib at the dose of 200 mg twice daily.

A 70-year-old male, known case of RCC, on treatment with oral sorafenib 200 mg twice daily for 30 days, presented with complaints of multiple painful fluid-filled lesions over palms and soles for 5 days. The patient had a history of tingling and burning sensation prior to the development of lesions over palms and soles. Cutaneous examination revealed multiple tender bullae over an erythematous base over bilateral palms [Figure 1] and soles [Figure 2]. The rest of the cutaneous examination was unremarkable. Histopathology of a blister from the left palm showed upper epidermal blister due to ballooning of keratinocytes and lymphocytic infiltrate in the upper epidermis [Figure 3]. Routine blood investigations were within normal limits. Based on the clinical features and histopathology, a diagnosis of HFSR secondary to sorafenib was made. Our case was diagnosed as grade 2 HFSR as per National Cancer Institute Common Terminology Criteria for Adverse Events v5.0 grading system [Table 1].[1] According to Hartwig's Severity Assessment Scale, this case was level 1 adverse drug reaction (ADR).[2] This ADR was probable as per Naranjo's score. As the clinical features were mild, the patient was continued with sorafenib treatment. The patient was treated with clobetasol propionate 0.05% ointment to apply twice daily over palms and soles along with moisturizers for 2 weeks. He was also advised to avoid contact with hot water and take analgesics and when required. There was a significant improvement of palmo-plantar lesions at the end of 2 weeks of local treatment [Figures 4 and 5].

Sorafenib, a small-molecule multikinase inhibitor with potent antiangiogenic, antiproliferative, and antineoplastic effects, is FDA approved for the treatment of advanced hepatocellular carcinoma, primary RCC, and thyroid carcinoma.[3-5] The systemic side effects of sorafenib are gastrointestinal, hyperthyroidism, hypertension, and hypoalbuminemia.[6] The dermatological side effects are acne, flushing, rash/desquamation, HFSR, alopecia, xerosis, facial erythema, splinter subungual hemorrhages, keratoacanthomas, leukocytoclastic vasculitis, epidermal inclusion cysts, and pruritus among which most common is rash/desquamation.[6-8] Sorafenib-induced HFSR is reported most commonly in 25-30% in patients who are on a standard dose, that is; 400 mg twice daily.[9] But in our case, it developed at a low dose (200 mg twice daily). It usually appears in the first 2-4 weeks of treatment and presents hyperkeratotic lesions with superficial blistering typically surrounded by a peripheral halo of erythema, usually affecting the flexural surfaces of the digits and the pressure areas of palms and soles.[10] The most widely accepted theory for the causation of HFSR is inhibition of platelet-derived growth factor receptor (PDGFR) and c-KIT receptors on human keratinocytes.[11] Being a tyrosine kinase inhibitor, it affects vascular endothelial growth factor (VEGF), VEGF receptor (VEGFR) and PDGFR, hence, the endothelium of the capillary vessels in the

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peripheral areas, including hand and foot areas are easily pressurized.[10] It is also excreted in the sweat glands resulting in direct skin toxicity, making palms, and soles most vulnerable for the reaction.[12] The dermatological side effects are dose dependant with doses equal to or more than 400 mg BD.[13] The lesions need to be differentiated from the classical chemotherapy-induced hand-foot syndrome (HFS) or palmoplantar erythrodysthesia seen with other chemotherapeutic agents such as capecitabine. Table 2 distinguishes between HFSR and HFS.[9,12,14] Histopathology

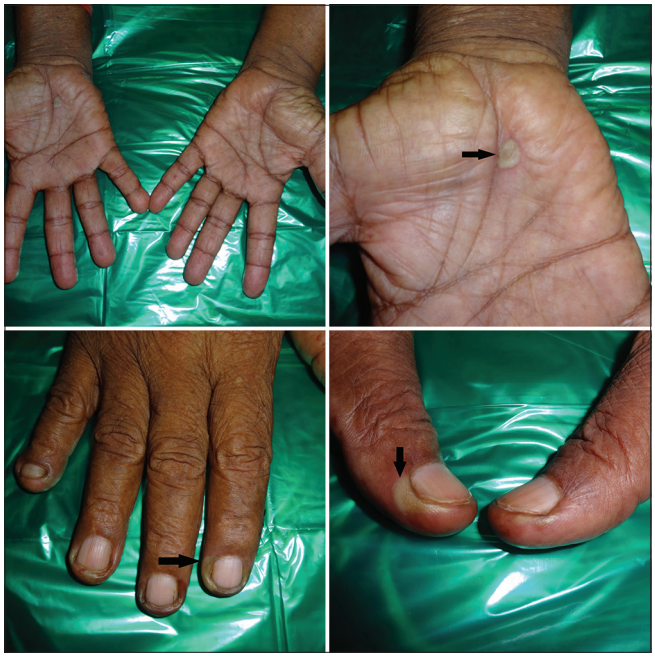

Figure 1: Multiple tender bullae (black arrows) over an erythematous base over palms and dorsa of fingers

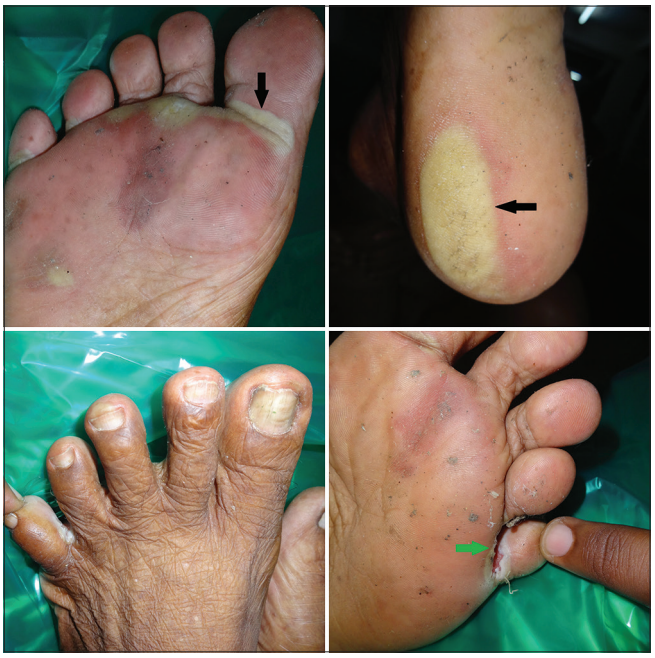

Figure 2: Multiple tender bullae (black arrows) over an erythematous base over soles with maceration of left fourth interdigital web space (green arrow)

Table 1: Grading of HFSR by CTCAE version 5.0 with treatment recommendations

Grade	Description	Prevention and treatment	Change in dose regimen
1	Minimal skin changes or dermatitis (e.g., erythema, edema, or hyperkeratosis) without pain	Avoid hot water, Use moisturizing creams, thick cotton gloves and/or socks, 20-40% urea	Maintain current dose of MKI
2	Skin changes (e.g., peeling, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting instrumental ADLs	As with grade 1; clobetasol 0.05% ointment; 2% lidocaine; codeine, pregabalin for pain topical calcipotriol	Dose reduction to 50% for 7-28 days
3	Severe skin changes (e.g., peeling, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting self-care ADLs	Treat as with grades 1 and 2	Interrupt treatment for 7 days and until improvement to grade 0-1

HFSR: Hand-foot skin reaction; CTCAE: Common terminology criteria for adverse events; MKI: Multikinase inhibitor; ADL: Activities of daily living

Table 2: Distinguishing features between HFSR and HFS

HFSR	HFS
Caused by multikinase inhibitors like sorafenib and sunitinib	Caused by classical chemotherapeutic agents like capecitabine, cytarabine, methotrexate, 5-fluorouracil
Less severe	More severe
Localized and sharply demarcated	Diffuse
Hyperkeratotic to erythematous edematous, painful and very tender blisters that evolve into inflamed and painful skin adjacent to the calluses	Less hyperkeratotic, usually diffuse erythema with edema and desquamation
Pressure exposed areas such as heels and metatarsal heads, friction, and weight-bearing sites	Less pressure exposed areas
Dose dependant	Dose independent
On histopathology, greater degree of epidermal replication and acanthosis seen	On histopathology, lesser degree of epidermal replication and acanthosis seen

HFSR: Hand-foot skin reaction; HFS: Hand-foot syndrome

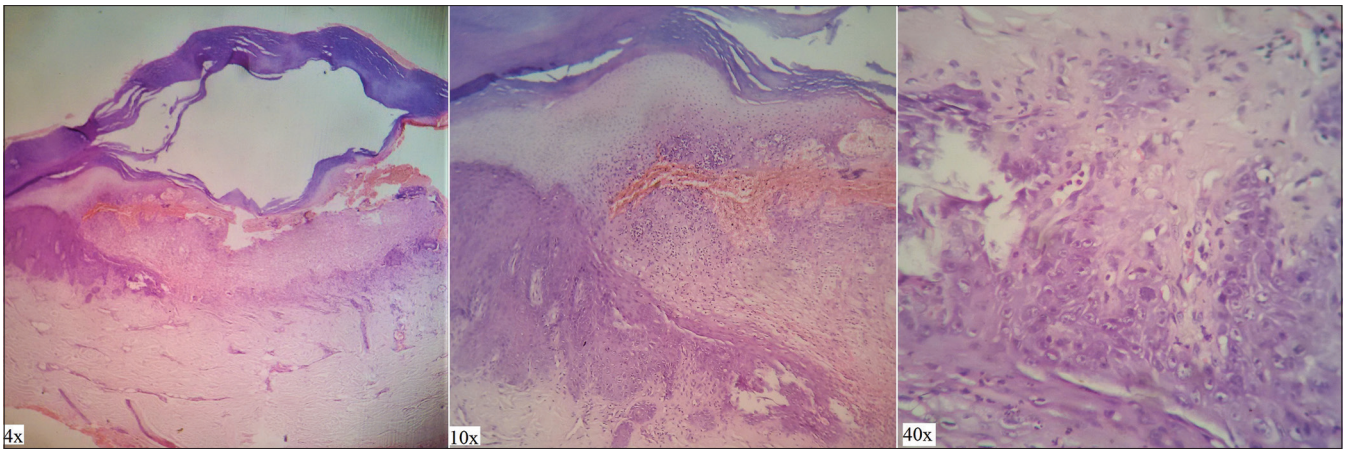

Figure 3: Upper epidermal blister due to ballooning of keratinocytes and lymphocytic infiltrate in the upper epidermis. (H and E, 4x, 10x, and 40x)

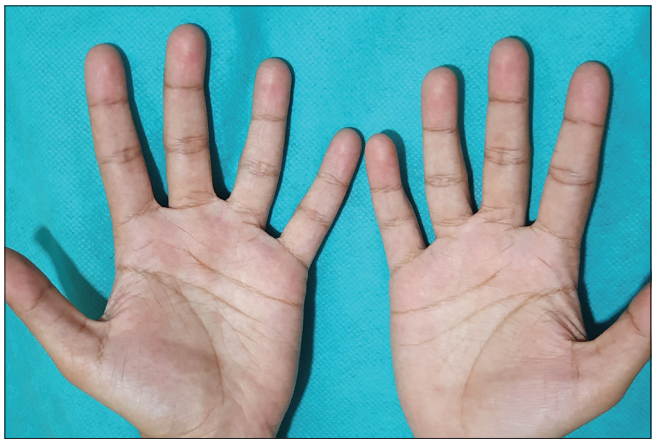

Figure 4: Complete resolution of lesions over palms after 2 weeks of treatment

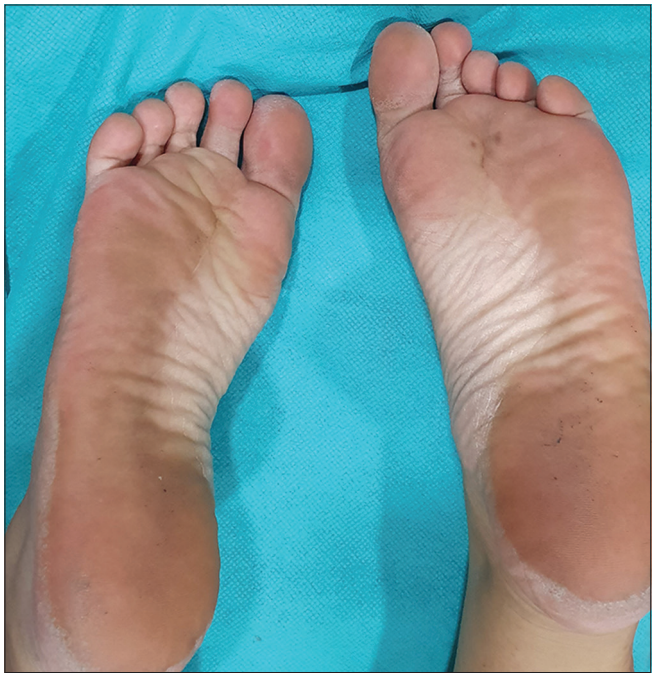

Figure 5: Complete resolution of lesions over soles after 2 weeks of treatment

Table 3: General measures and treatment options for HFSR

Hands and feet to be kept away from water
Avoidance of tight clothing, friction, and activities that expose them to hard contact with objects
To wear soft-bottomed and open shoes during treatment
Use of alcohol-free moisturizers immediately after bathing
Petroleum gels and humectants containing urea and salicylic acid for hyperkeratotic lesions
Topical steroids to reduce inflammation, pain, and erythema
Analgesics, pregabalin, and topical lidocaine to reduce pain
Topical calcipotriol

shows epidermal keratinocyte apoptosis, dyskeratosis, and vacuolar degeneration with intraepidermal blister formation followed by massive acanthosis, papillomatosis, and parakeratotic hyperkeratosis,[15] as seen in our case. According to Schumock and Thornton's criteria for ADR preventability assessment, sorafenib-induced HFSR is definitely preventable ADR.[16] Various treatment options for HFSR are highlighted in Table 3.[6,10,12] Topical calcipotriol in HFSR was first used by Demirkan *et al.* in sorafenib HFSR considering that it binds to the vitamin D receptors and inhibits keratinocyte proliferation and converts the differentiation into the normal course, thus, can be used as a good therapeutic agent.[14] New preventive drug to prevent sorafenib-induced HFSR includes ingestion of dried bonito broth (DBB) which maintains blood flow. Ingestion of DBB 1 week prior to sorafenib initiation prevents HFSR.[17]

Conclusion: Thus, sorafenib-induced HFSR is a dose dependant reaction but we report this case due to its occurrence at a low dose (200 mg BD) in our report.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The

patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

References

1. National Cancer Institute Cancer Therapy Evaluation Program. Common Terminology Criteria for Adverse Events [v5.0]. 27-11-2017.
2. Srinivasan R, Ramya G. Adverse drug reaction-causality assessment. Int J Res Pharamc Chem 2011;1:606-12.
3. Finn RS. Drug therapy: Sorafenib. Hepatology 2010;51:1843-9.
4. Strumberg D, Richly H, Hilger RA, Schleucher N, Korfee S, Tewes M, *et al*. Phase I clinical and pharmacokinetic study of the Novel Raf kinase and vascular endothelial growth factor receptor inhibitor BAY 43-9006 in patients with advanced refractory solid tumors. J Clin Oncol 2005;23:965-72.
5. Sil A, Das NK. Sorafenib-induced hand-foot syndrome in a patient of renal cell carcinoma. Indian J Pharmacol 2014;46:334-6.
6. Robert C, Mateus C, Spatz A, Wechsler J, Escudier B. Dermatologic symptoms associated with the multikinase inhibitor sorafenib. J Am Acad Dermatol 2009;60:299-305.
7. Kong HH, Cowen EW, Azad NS, Dahut W, Gutierrez M, Turner ML. Keratoacanthomas associated with sorafenib therapy. J Am Acad Dermatol 2007;56:171-2.
8. Chung NM, Gutierrez M, Turner ML. Leukocytoclastic vasculitis masquerading as handfoot syndrome in a patient treated with sorafenib. Arch Dermatol 2006;142:1510-1.
9. Susan D, Malini M, Reghu R. Sorafenib induced hand and foot syndrome. J Young Pharm 2018;10:129-30.
10. Lacouture ME, Wu S, Robert C, Atkins MB, Kong HH, Guitart J, *et al*. Evolving strategies for the management of hand-foot skin reaction associated with the multitargeted kinase inhibitors sorafenib and sunitinib. Oncologist 2008;13:1001-11.
11. Lee WJ, Lee JL, Chang SE, Lee MW, Kang YK, Choi JH, *et al*. Cutaneous adverse effects in patients treated with the multitargeted kinase inhibitors sorafenib and sunitinib. Br J Dermatol 2009;161:1045-51.
12. Bansal S, Sardana K, Singh K, Garg VK. Concurrent hand-foot skin reaction and hair depigmentation with sunitinib: Report of a case and literature review of kinase inhibitors and blocking antibodies. Indian J Dermatol 2014;59:588-91.
13. Autier J, Escudier B, Wechsler J, Spatz A, Robert C. Prospective study of the cutaneous adverse effects of sorafenib, a novel multikinase inhibitor. Arch Dermatol 2008;144:886-92.
14. Demirkan S, Gündüz Ö, Devrim T. Sorafenib-associated hand-foot syndrome treated with topical calcipotriol. JAAD Case Rep 2017;3:354-7.
15. Segaert S, Chiritescu G, Lemmens L, Dumon K, Van Cutsem E, Tejpar S. Skin toxicities of targeted therapies. Eur J Cancer 2009;1:295-308.
16. Schumock GT, Thornton JP. Focusing on the preventability of adverse drug reactions. Hosp Pharm 1992;27:538.
17. Kamimura K, Shinagawa-Kobayashi Y, Goto R, Ogawa K, Yokoo T, Sakamaki A, *et al*. Effective prevention of sorafenib-induced hand-foot syndrome by dried-bonito broth. Cancer Manag Res 2018;10:805-13.