IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 22, Issue 6 Ser.2 (June. 2023), PP 36-40
www.iosrjournals.org

Kinase Inhibitors Induced Cutaneous Reactions In Patients With Hepatocellular Carcinoma – A Case Series.

Preetham Pottipati[1], Selvasudha[2], Ganesa Sooria K[3], Kabilan N[4.]
[1]*assistant professor, corresponding author, department of DVL, KIMS&RC.*
[2]*associate professor,*
[3]*assistant professor,*
[4]*Junior resident.*

Abstract:
Introduction: *Multi Kinase Inhibitors (MKI) like Sorafenib, Lenvatinib are a group of drugs used in the treatment of patients with Hepatocellular carcinoma (HCC), advanced renal cell carcinoma, thyroid malignancies. The main mechanism of action consists of inhibition of Vascular endothelial growth factor receptors (VEGFRs), Fibroblast growth factor receptors, KIT, Platelet derived growth factor receptors (PDGF), RET.*
Key words: *Lenvatinib, Sorafenib, kinase inhibitors, Cutaneous drug reaction, HCC.*

Date of Submission: 22-05-2023 Date of Acceptance: 02-06-2023

I. Background :

Patients aged around 60 years of Indian origin, presented to our dermatology outpatient department in a tertiary care center, one on treatment with Sorafenib and other with Lenvatinib, presented with history of progressive, pruritic, erythematous papulo-squamous rash. On examination patient 1had tender desquamative lesions over palms and soles. They also have developed bullous eruption over the lateral side of both feet, dorsum of ankle joint and foot. The patient had undergone partial Hepatectomy and cholecystectomy and was on treatment with Sorafenib for a duration of 12 months and other patient was an old case of advanced HCC, who is on Lenvatinib for 2 months.

On detailed cutaneous examination, patient 1 had numerous pruritic psoriasiform plaques over thighs (Fig 5), and perianal region and perineum. This patient also had bullous eruption over the lateral and posterior aspect of bilateral foot, dorsum of ankle joint and dorsum of foot. He had tender eczematous and erythematous plaques over the flexor aspect of phalangeal joints over bilateral palmar surface (Fig 2), and bullous eruption over the dorsum of foot and posterior and lateral aspect of calcaneum, which are consistent with hand-foot-skin reaction (HFSR) (Fig 1,4). The patient had multiple eruptive cherry hemangioma over anterior and posterior aspect of chest and abdomen (Fig 9). He also had multiple lichenified plaques and callosities over dorsal aspect of both feet and posterior aspect of calcaneal region (Fig 3).

Patient had developed multiple senile Comedones over zygomatic area, seborrheic keratosis and acneiform eruptions over the face (Fig 7). He also had erythematous papules over forehead (Fig 7). On genital examination patient had erythematous rash over bilateral cruris, perineum and perianal region (Fig 8).

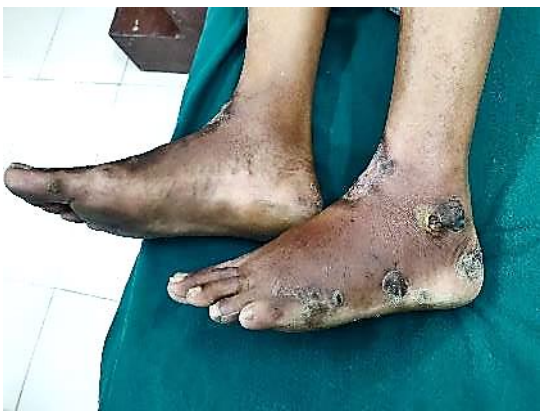


Fig 1,2: HFSR- Hand Foot Skin reaction

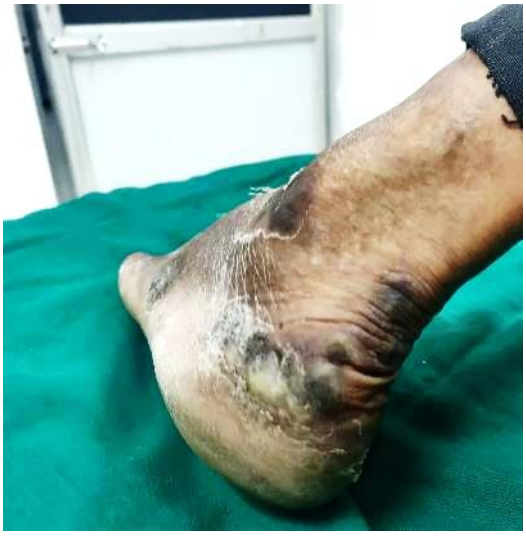


Fig 3: Callosities

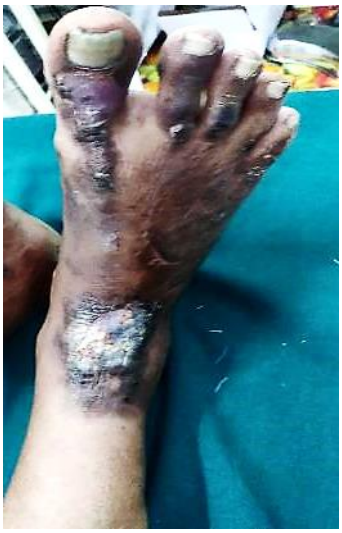


Fig 4: HFSR – Hand Foot Skin reaction.

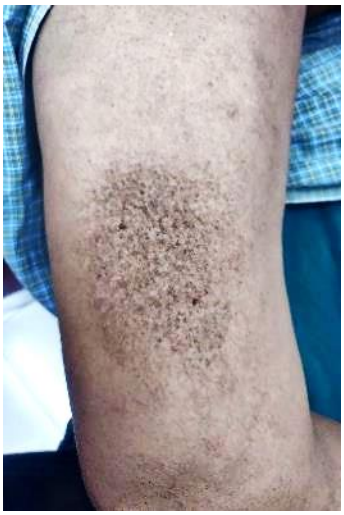


Fig 5,6: Psoriasiform eruption on thigh and dorsum of hand, knuckles

Fig 7: Senile comedones & acneiform eruptions

Fig 8: Perianal and perineal dermatitis

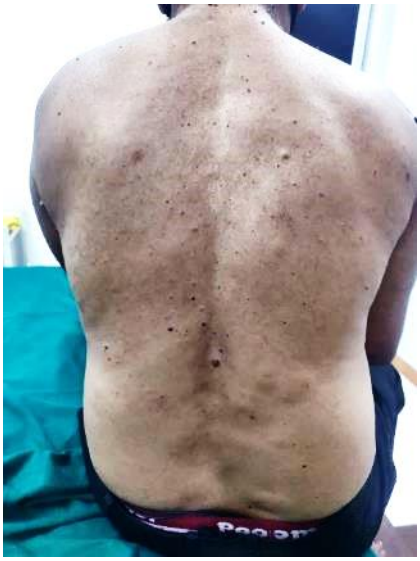


Fig 9: Eruptive cherry hemangiomas

A skin biopsy was taken from lower limb and the histopathological findings of hand-foot skin reaction include keratinocyte vacuolar degeneration, the presence of intracytoplasmic eosinophilic bodies, and intraepidermal blisters. The patient was treated with mild systemic steroid, topical antibiotic and potent corticosteroid, with moderate relief from the symptoms. Patient has been changed to Lenvatinib 4 mg bd for 3 months and he had recurrence of similar symptoms.

Another Patient who was on treatment with Lenvatinib for a duration of 4 weeks, presented with severely painful, tender palms. He was complaining of difficulty with daily activities and inability to hold objects. On examination the patient had desquamative bullous eruption over the palmar surface of both palms with oozing lesions over the dorsum of foot, consistent with Hand Foot Skin Reaction (HFSR)(fig 10). The patient also had psoriasiform lesions over the dorsal aspect of proximal interphalangeal joints of both hands(fig 12).

Fig 10,11,12: HFSR & psoriasiform eruptions

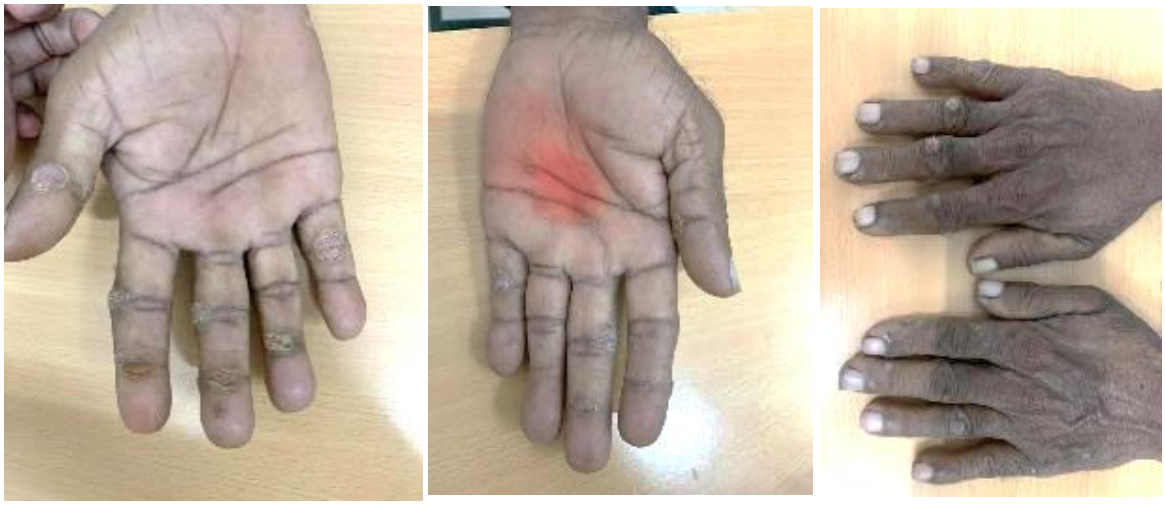
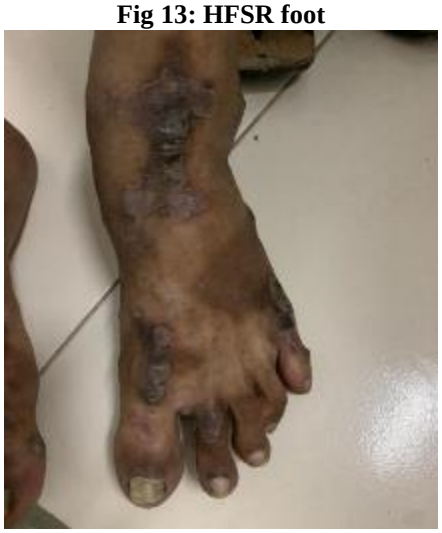


Fig 13: HFSR foot



II. Discussion:

Sorafenib and Lenvatinib are two related Multi Kinase inhibitors (MKI's) which act to inhibit VEGFR-1,2,3, PDGFR-β, RET and KIT. VEGF signaling pathway is the key pathway of vasculature of different tumors which helps in mediating endothelial cell proliferation, vascular permeability, vasodilation and tumor migration and its neovascularization[1].

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

HFSR manifests as palmoplantar lesions, and especially in exposed areas. These lesions can have a significant detrimental effect on a patient's quality of life. HFSR induced by sorafenib use mimics classic HFS. Classic HFS which is also known as acral erythema or palmar-plantar erythron-dysesthesia, and this occurs during the use of various other chemotherapeutic agents, like cytarabine, doxorubicin, capecitabine and 5 fluorouracil. The incidence of HFS ranges from 7% to 70%, depending on the type of chemotherapeutic agent being used[4]. HFSR caused by sorafenib mimics several of the non-specific clinical and pathological features consistent of classic HFS. These include paresthesia or pain and tenderness, erythema, fissures and non-specific pathological inflammatory infiltrates along with features of lichenoid dermatitis. However, sorafenib-induced HFSR is the most commonly associated with palmar and/or plantar hyperkeratosis[5].

The treatment for HFSR include the use of emollients, topical corticosteroids and keratolytics such as urea, lactic acid and salicylic acid[9]. It is recommended that patients who have severe HFSR may have their

sorafenib dose adjusted, without subsequent treatment interruption. HFSR can develop immediately after sorafenib is initiated. These patients who develop HFSR within first 2-4 weeks of initiating sorafenib therapy are especially in need of proper medical management to relieve symptoms, improve the quality of life and to prevent progression to higher-grade HFSR[6].

VEGF has been implicated in pathophysiology of psoriasis as it is overexpressed on psoriatic keratinocytes, this contributes to hyperplasia of 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 the treatment with sorafenib and sunitinib, is causing remission of existing chronic plaque psoriasis.

Hypotheses for sorafenib-induced psoriasiform reactions include the hypoxia-inducible factor pathway, which is an upstream of 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 cleared and may differ between MKIs, due to the diversity in their target action and affinities with different immunomodulatory effects[9].

Other cutaneous effects like Palmoplantar hyperkeratosis, keratosis pilaris–like eruption, multiple cysts, eruptive keratoacanthomas, and squamous cell carcinoma have also been described in patients on treatment with sorafenib, which support the hypothesis that the sorafenib alters keratinocyte proliferation, differentiation and neo angiogenesis[10].

III. Conclusion:

Multi kinase inhibitors, including sorafenib, can 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 can be continued uninterrupted. Observations, as in this case described, can contribute to a better understanding of the side effects and aid physicians in the early management of these patients.

References:

[1]. Wilhelm SM, Adnane L, Newell P, Villanueva A, Llovet JM, Lynch M. Preclinical overview of sorafenib, a multikinase inhibitor that targets both Raf and VEGF and PDGF receptor tyrosine kinase signaling. Mol Cancer Ther. 2008-3129-40.
[2]. Padda IS, Parmar M. Lenvatinib. [Updated 2022 Jul 12]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK567768/
[3]. Cohen PR. Sorafenib-associated facial acneiform eruption. Dermatol Ther (Heidelb). 2015:77-86.
[4]. Kwakman JJM, Elshot YS, Punt CJA, Koopman M. Management of cytotoxic chemotherapy-induced hand-foot syndrome. Oncol Rev. 2020-14(1):442.
[5]. Kim DH, Son IP, Lee JW, Lee HI, Kim BJ, Kim MN. Sorafenib (Nexavar®, BAY 43-9006)-induced Hand-foot Skin Reaction with Facial Erythema. Ann Dermatol. 2011:119-22.
[6]. McLellan B, Ciardiello F, Lacouture ME, Segaert S, Van Cutsem E. Regorafenib-associated hand-foot skin reaction: practical advice on diagnosis, prevention, and management. Ann Oncol. 2015:2017-26.
[7]. Man XY, Yang XH, Cai SQ, Bu ZY, Zheng M. Overexpression of vascular endothelial growth factor (VEGF) receptors on keratinocytes in psoriasis: regulated by calcium independent of VEGF. J Cell Mol Med. 2008:649-60.
[8]. Sally R, Ugonabo N, Nguyen A, Kim RH, Lo Sicco K. Lenvatinib-induced psoriasiform eruption and palmoplantar erythema in a patient with hepatocellular carcinoma. JAAD Case Rep. 2021;15:1-3.
[9]. Weidemann AK, Crawshaw AA, Byrne E, Young HS. Vascular endothelial growth factor inhibitors: investigational therapies for the treatment of psoriasis. Clin Cosmet Investig Dermatol. 2013:233-44.
[10]. Courtney J. Ensslin, MD; Pei-han Kao, MD; Ming-ying Wu, MD, Psoriasiform drug eruption secondary to sorafenib: case series and review of the literature. Cutis. 2019;104:E11-5.