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Hand-foot skin reaction with primarily dorsal involvement in a patient with metastatic renal cell carcinoma on cabozantinib

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Abstract

A 61-year-old man with metastatic renal cell carcinoma on cabozantinib developed hand-foot skin reaction with predominantly dorsal involvement including painful violaceous plaques over the joints and keratotic yellow plaques on the palmar fingers. The medication was discontinued with resolution of the plaques and later reinitiated at a lower dose uneventfully.

Keywords: cabozantinib, hand foot skin reaction, renal cell carcinoma, drug reaction, chemotherapy reaction

Case Synopsis

A 61-year-old man with metastatic renal cell carcinoma presented to dermatology clinic with indurated, exquisitely tender, dusky purple plaques over the dorsal interphalangeal and metacarpophalangeal joints and eroded yellow plaques on the frictional palmar surfaces (**Figure 1**). Pain and edema limited mobility. One month prior the patient had undergone one cycle of cabozantinib at 66.7% dose reduction (40mg). It was well tolerated with some mild erythema of the dorsal hand joints and tenderness at frictional surfaces of the palms and soles. A second cycle at full dosage (60mg) was started 7 days prior to his presentation.

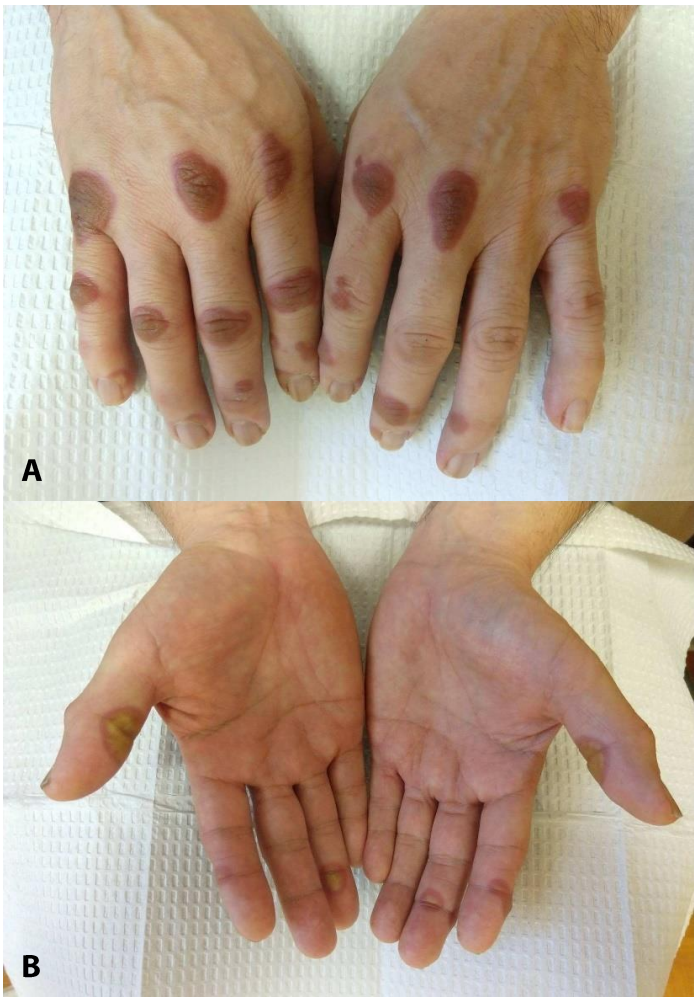

Figure 1. ***A)*** *Dorsal hands reveal dusky purple tender calluses over the interphalangeal and metacarpophalangeal joints with some generalized edema and swelling.* ***B)*** *Palmar hands with numerous exquisitely tender yellow, cracked calluses in areas of friction and movement.*

A punch biopsy was performed revealing regular acanthosis, parakeratosis, corneal neutrophils, and prominent dyskeratosis (**Figure 2**). Periodic acid-Schiff stain was negative for fungal elements. These findings favored hand-foot skin reaction (HFSR). Based on these findings, cabozantinib was stopped. One month after discontinuation the patient demonstrated resolution of the plaques. Cabozantinib was resumed at a 33.3% dose reduction (20mg) without recurrence of skin lesions.

Case Discussion

Cabozantinib is an inhibitor of numerous pro-invasive receptor tyrosine kinases, including VEGFR-1,-2 and -3, FLT-3, KIT, RET, and TIE-2. This multikinase inhibitor (MKI) induces apoptosis of cancer cells and suppress tumor growth, metastasis, and angiogenesis [1]. It is currently FDA approved for metastatic medullary thyroid cancer, advanced renal cell carcinoma, and advanced hepatocellular carcinoma.

Skin reactions are estimated to occur in 73% of patients on cabozantinib and include HFSR (54%), generalized pigment dilution or hair depigmentation (44%), xerosis (20%), scrotal erythema or ulceration (15%), and nail splinter hemorrhages (12%), [2]. Approximately 1/3 of patients experience grade 3 or 4 reactions.[3] According to the NIH Common Terminology Criteria for Adverse Events (NIH-CTCAE v5.0), grade 3-4 maculopapular rashes cover >30% body surface area (BSA) with moderate or severe symptoms that limit self-care and activities of daily living; the majority of cases present with local superinfection requiring antibiotics (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf, accessed January 11, 2020). Cabozantinib-related reactions typically occur by the first (57%) or second (80%) month of therapy [2]. Dose reduction may be needed in 30% of patients and a small portion may require drug discontinuation.

Hand-foot skin reaction is a commonly reported sequela of cytotoxic chemotherapeutic agents and MKIs. Chemotherapy- and MKI-induced HFSR each have unique presentations [2]. Chemotherapy-associated HFSR typically presents with diffuse palmoplantar erythema. In contrast, MKI-associated HFSR presents with bilateral, painful, callus-like hyperkeratosis with edema and erythema. These are generally palmoplantar and in areas of increased friction, pressure, and mechanical stress. This case is notable as it primarily involved the dorsal aspects of the hands, a distribution not previously well-documented.

Histologically, lesions of MKI-associated HFSR present with epidermal acanthosis and papillomatosis, parakeratosis, dyskeratosis, and vacuolar degeneration of keratinocytes. Intracytoplasmic eosinophilic bodies and intraepidermal vesicles may be present [4]. Biopsies may demonstrate superficial telangiectasias, mild superficial perivascular lymphocytic infiltrate, and dysmorphic eccrine cells with cystic changes in the

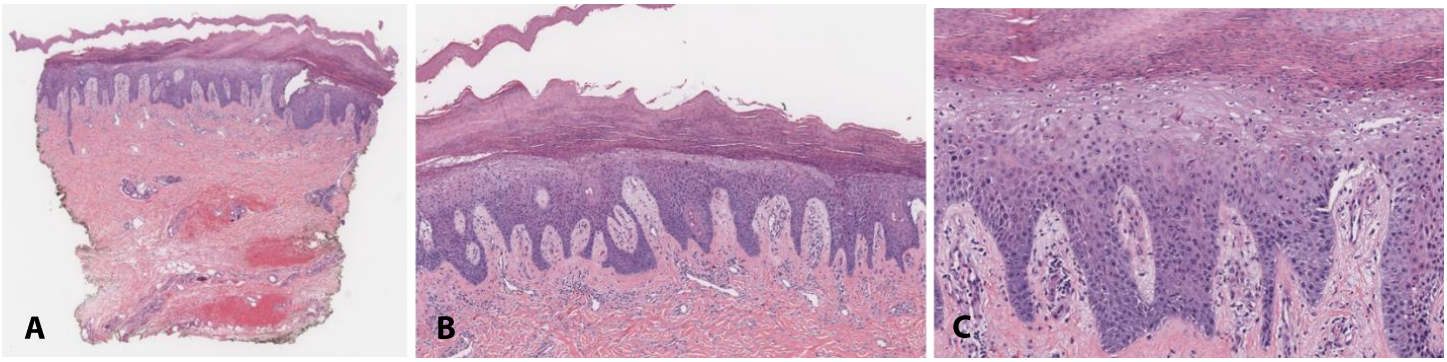

Figure 2. ***A)*** *Punch biopsy reveals prominent hyperkeratosis and parakeratosis in the stratum corneum consistent with the patient being in his second month of therapy.* ***B)*** *Parakeratosis and hyperkeratosis are accompanied by a mild superficial perivascular lymphocytic infiltrate and pallor in the upper layers of the epidermis.* ***C)*** *Scattered necrotic keratinocytes are present through the upper layers of the epidermis. H&E,* ***A)*** *40x,* ***B)*** *40x,* ***C)*** *400x.*

eccrine glands. It is believed that the depth of keratinocyte alteration in the epidermis correlates with the time of exposure to the MKI. Patients on therapy for <30 days demonstrate dyskeratosis in the stratum spinosum and granulosum, whereas patients treated for ≥30 days show hyperkeratosis and parakeratosis in the stratum corneum [5]. Our patient demonstrated prominent parakeratosis and dyskeratosis and was in his second month of therapy.

The pathogenesis of HFSR may be related to toxic drug concentrations in acral sweat glands or capillary microtrauma leading to leak of drug into tissues and accumulation of toxic breakdown products. Hand-foot skin reaction typically resolves rapidly after cessation of the medication, making it more tolerable in short-term regimens [2]. However, MKIs like cabozantinib are generally prescribed for long-term treatment, resulting in frequent treatment dilemmas.

Management options are limited but dose-modification or discontinuation of cabozantinib typically leads to rapid resolution of HFSR lesions. However, this is achieved at the risk of diminishing cancer response to therapy and must be weighed carefully. Patients have been advised to minimize mechanical stress, friction, and extreme temperatures to the hands and feet. Cotton socks and gel inserts can be helpful to minimize friction to the feet. Topical application of salicylic acid or urea along with mechanical paring can be helpful to treat hyperkeratosis. Paring must be performed cautiously to avoid infection. High-potency topical corticosteroids may also be helpful in the setting of inflammation or erythema [2].

Conclusion

In conclusion, we present a 61-year old man with metastatic renal cell carcinoma who developed TKI-induced hand-foot skin reaction with predominantly dorsal involvement including painful violaceous plaques over the joints and keratotic yellow plaques on the palmar fingers in the setting of taking the medication cabozantinib. The medication was discontinued with resolution of the plaques and later restarted at a lower dose uneventfully. The patient was well at last follow-up with stable burden of malignancy

Potential conflicts of interest

The authors declare no conflicts of interests.

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