Painful Rashes on the Palms and Soles

A 72-year-old male of Caucasian descent was referred for consideration of systemic therapy after receiving a diagnosis of hepatocellular carcinoma (HCC). His past medical history was unremarkable with no comorbidities and he was not on any other medications. Computer tomography (CT) scan revealed multifocal HCC, and a biopsy of which confirmed HCC. There was no underlying cirrhosis or features of portal hypertension. His viral hepatitis profile was negative, as were his autoimmune screen. His iron studies, copper levels and thyroid function were all in the normal range. He was well with a performance status of Eastern Cooperative Oncology Group (ECOG) 0. He was started on a trial of sorafenib at a dose of 400 mg twice daily. Nine weeks later, he presented with well demarcated, tender well defined yellowish hyperkeratotic plaques on his plantar surfaces (Fig. 1) and erythematous patches on the palmar surfaces (Fig. 2). It gradually spread to the arms and legs forming pustules and blisters with raw ulcerated surfaces.

What is the most likely diagnosis of his skin condition?

A. Plaque psoriasis
B. Pityriasis rubra pilaris
C. Cutaneous infiltration of malignancy
D. Keratoderma blennorrhagica
E. Palmar-plantar erythrodysesthesia

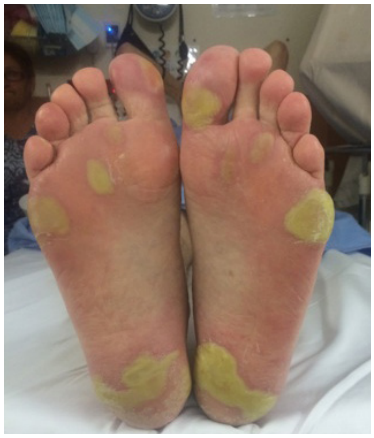

Fig. 1. Symmetrical hyperkeratotic yellow plaques on the plantar surfaces of the soles.

Discussion

Hand-foot syndrome (HFS) or palmar-plantar erythrodysesthesia is an adverse cutaneous reaction seen with multikinase antineoplastic therapy. In our patient, sorafenib which has been approved for use in the treatment of HCC and renal cell carcinomas was the causative drug. Other anticancer drugs commonly implicated in HFS are capecitabine and 5-FU.[1]

Sorafenib is a molecule capable of multilevel kinase inhibition, simultaneously inhibiting molecular components of the Raf-MEK-ERK signalling pathway, abrogating tumour growth and vascular endothelial growth factor receptor (VEGFR-1, VEGFR-2, VEGFR-3,) and platelet-derived growth factor receptor (PDGFR-β). This gives the drug a pro-apoptotic and anti-angiogenic effect.[2] The safety and efficacy of sorafenib in treating HCC was established in the Phase III SHARP Trial (Sorafenib in Advanced Hepatocellular Carcinoma) in patients with advanced disease if they were not eligible for or have had disease progression after surgical or locoregional therapies.[3] In the SHARP Trial, 21% of patients developed HFS and it was severe (grade 3) in 8%. This drug-related adverse event has been previously observed in its use in the treatment of renal cell carcinoma, leading to dose reductions and interruptions in a subgroup of patients.[4]

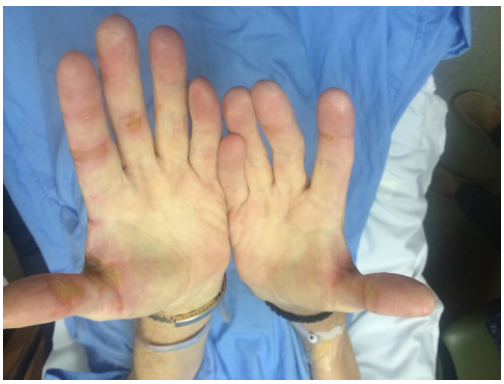

Fig. 2. Palmar erythema were more pronounced on the finger pads.

Answer: E

The diagnosis of HFS is a clinical one based on the temporal relationship with the drug and typical clinical presentation. The pathogenesis remains unclear at present. There are 3 grades used to assess the severity of the lesions. Grade 1 lesions are palmar erythema predominantly on the finger pads and yellow hyperkeratotic plaques with erythematous borders on pressure-bearing areas of the soles.[1] Grade 2 lesions present as palmar erythema with superficial desquamation or tense bullae with mild background erythema.[1] Grade 3 lesions are described as markedly erythematous plaques with discrete, tense bullae.[1] The severity of the lesions tend to be dose-related. In some cases, HFS may have a profound negative impact on the patients' quality of life (QoL). The HFS-14, is a validated tool for the QoL assessment in HFS patients.[5] It can be used by treating physicians to guide them on the appropriate next steps.

HFS side effects have been investigated to correlate to treatment efficacy. In some drugs such as cetuximab and panitumumab in metastatic colorectal cancer, skin rash represents a significant predictor of the efficacy of the drugs.[6,7] The occurrence of skin toxicity represents a predictive factor for survival (HR 0.51; P <0.00001) and progression (HR 0.58; P <0.00001). Similarly, patients who developed moderate or severe rash had an increased chance of response (35 vs 13%; RR 2.23, P <0.00001).[6,7] However, even though it is recognised that skin rash is a common side effect of sorafenib, its ability to serve as a surrogate biomarker for drug efficacy is difficult because the drug has a relatively low objective response rate (ORR) in the order of 2% to 3%.[3]

Two retrospective studies, one conducted in Japan and the other in South Korea, revealed that the occurrence of skin toxicities during sorafenib treatment in HCC is associated with improved overall survival (OS).[8,9] However, a retrospective analysis of skin toxicities during the treatment trial period may have been confounded by an inherent observation bias because patients who are treated for longer periods may be at a greater risk of experiencing toxicities.[8-10] Vincenzi et al[11] examined associations between treatment outcomes and skin toxicities within the first month of treatment. Sixty-five patients who received sorafenib for advanced HCC were enrolled, and early all-grade skin toxicities predicted a significantly improved disease control rate (DCR) and time to progression (TTP) and prolonged OS with borderline significance. The clinical value of an association between skin rash and efficacy remains to be established and further studies need to be done to validate its use as a reliable and predictable biomarker in clinical practice.

Treatment options for HFS vary according to the severity of the lesions. In milder cases, topical therapy consisting of keratolytics, topical steroids and emollients would suffice. In the more severe cases, the causative drug would have to be discontinued as the lesions have the tendency to progress while the patient is on chemotherapy. In our patient, we opted to cease treatment indefinitely. After a 2-week period of cessation of therapy, the rash showed some degree of improvement.

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