To the Editor:

Sorafenib is a new oral drug currently approved for the treatment of metastatic renal cell carcinoma and hepatocellular carcinoma. The drug acts partly by inhibiting the tyrosine kinase receptors implicated in angiogenesis and tumor progression, and partly by blocking Raf kinase pathways. Up to 90% of patients receiving this treatment are reported to develop dermatological side-effects. Hyperkeratosis-like lesions commonly appear on the pressure pads of palms and soles and this may require withdrawal of the medication in more serious cases.1,2

Palmoplantar Cutaneous Reaction to Sorafenib

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The patient was a 62-year-old man, with a medical history of diabetes mellitus treated with oral antidiabetic agents, and metastatic renal cell carcinoma treated with sorafenib at a dose of 400 mg twice daily for the previous 4 weeks. He consulted for some very painful and disabling lesions on the finger flexures and interdigital areas of the hands that had appeared 3 days previously (Figure 1).

Physical examination revealed yellowish hyperkeratotic plaques with a symmetrical erythematous halo that took on the form of tense blisters in some areas.

A 4 mm punch biopsy was taken of one of the lesions. Histology showed a superficial perivascular and periadnexal lymphocytic infiltrate that lacked atypical features and that was far more abundant at the dermal-epidermal junction. The epidermis displayed marked spongiosis, with the formation of intracytoplasmic vesicles and vacuolar degeneration of keratinocytes in the upper levels (Figure 2).

Topical treatment with clobetasol propionate ointment was prescribed and the discomfort and lesions resolved in 2 weeks without the need to suspend oncology treatment.

Sorafenib is a new oral chemotherapy treatment. It acts by inhibiting various kinase receptors including endothelial growth factors 2 and 3, transforming growth factor-β and c-kit, and blocking the Raf pathway.1-3 Its use has currently been approved for metastatic renal cell carcinoma and hepatocellular carcinoma, and research is being undertaken into its application to breast cancer, non-small cell lung cancer and melanoma.

Dermatological manifestations are the most common side-effects, although the pathogenic mechanism is not entirely clear at present.

Palmoplantar cutaneous reaction is one of the most common side-effects (30%).4 This is characterized by paresthesia, pain, and discomfort that may even lead to immobilization or the inability to handle objects, followed by the appearance of yellowish hyperkeratotic plaques in the pressure areas—mainly on the palms, but also on the soles (Table 1).

This is clinically similar to the palmoplantar erythrodysesthesia caused by other oncology drugs such as capecitabine, cytarabine, doxorubicin, and fluorouracil.5,6 The differences are however that sorafenib-induced reaction tends to be hyperkeratotic and localized, occurring in the pressure areas with mild involvement, while palmoplantar erythrodysesthesia does not tend to...
be hyperkeratotic (except in chronic phases), has a diffuse
distribution, and tends to be more serious.

Sunitinib—a treatment from the same family as
sorafenib that also acts by inhibiting kinase receptors
implicated in angiogenesis and tumor progression—is
also known to generate similar palmoplantar cutaneous
reactions.

In histological terms, some authors have considered
vacuolar degeneration of keratinocytes, the presence of
intracytoplasmic eosinophilic bodies, and the formation
of vesicles in the Malpighian layer to be the most relevant
features.7

These tend to be mild lesions (grade 1/2) that respond
to topical treatment with urea and salicylic acid emollient
crèmes and high potency corticosteroids. Occasionally,
the presence of severe lesions (grade 3/4) may mean
that doses of oncology drugs will need to be halved or
administration suspended temporarily until the lesions
have healed. The lesions do not generally reappear when
treatment is reinitiated.

Other dermatological side-effects include: asymptomatic
subungal splinter hemorrhages (60%)2 in patients treated
with both sorafenib and sunitinib; a scaly erythematous
facial eruption (63%)1 that resembles an outbreak of
seborrheic dermatitis and resolves spontaneously; varying
degrees of rash; alopecia (27%)4 with regrowth during
treatment or after withdrawal; and cutaneous xerosis
mostly on the lower limbs (10%-20%).2

It is important that patients be made aware of the
higher frequency of dermatological side-effects produced
by this new oncology treatment—including cases of
palmoplantar cutaneous reaction like the one seen above.
They should be provided with preventive guidance on
hygiene, appropriate clothing, and footwear. Where the
lesions do occur, appropriate topical treatment should
be prescribed and the decision made on whether or not
to reduce the dose or temporarily suspend medication
(Table 2).

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