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## Dermatologic Toxicity to Sorafenib

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### To the Editor:

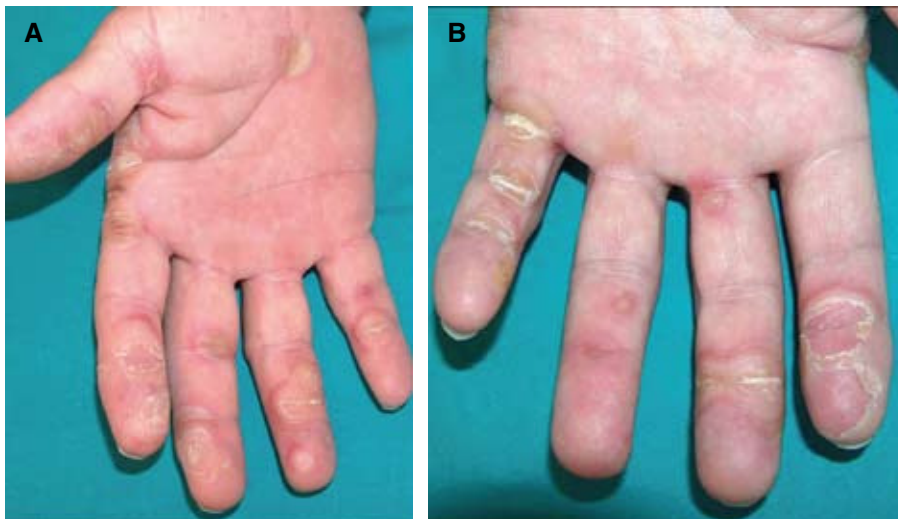
Sorafenib is a recent orally administered drug in the family of tyrosine kinase inhibitors; it has proved highly effective in the treatment of advanced renal cell and hepatocellular carcinomas.<sup>1</sup> Current research is investigating its application in the treatment of other tumors, such as metastatic melanoma or papillary thyroid carcinoma.<sup>2</sup> However, as with all chemotherapy drugs sorafenib has adverse effects, both systemic and dermatological. More than 93% of patients receiving sorafenib in monotherapy will suffer from some form of skin reaction.

We present the case of a 53-year-old man, diagnosed with hepatocellular carcinoma secondary to chronic liver disease due to hepatitis C virus infection, who began treatment with sorafenib at a dose of 400 mg twice a day. After 2 weeks of treatment, the patient began experiencing slightly painful skin lesions on the palms of the hands

and later on the soles of the feet, with no associated neurological symptoms. Physical examination revealed papules and plaques—some targetoid, edematous, and desquamative—located on the palms, the palmar surface of the fingers, and the soles of the feet (Figure 1).

Histology of tissue taken from a palmar lesion revealed a thick, orthokeratotic corneal layer in the epidermis, with an underlying area of parakeratosis and significant irregular acanthosis. Occasional necrotic keratinocytes were identified, with no sign of vacuolar degeneration of the basal layer. The blood vessels nearest the surface of the dermis were dilated and accompanied by a mild lymphocytic and histiocytic infiltrate (Figures 2 and 3).

The clinical findings and temporal relationship with the administration of sorafenib led to treatment with topical corticosteroids and a reduction of the drug dosage by half. This resulted in good response and progressive resolution of the skin lesions.



**Figure 1.** Edematous, desquamative papules and plaques in a symmetrical distribution on the palms and the soles of feet.

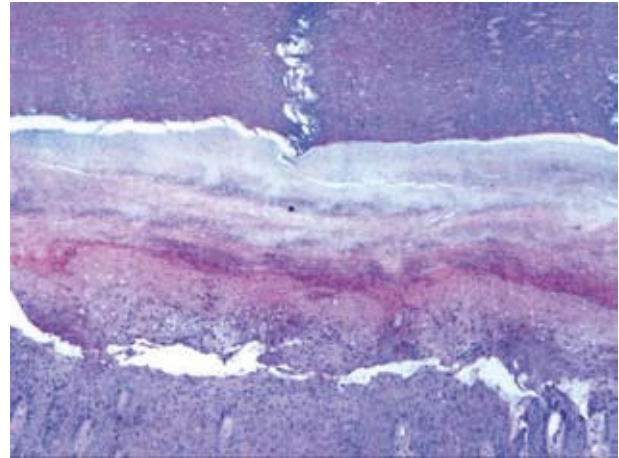
As small molecules or monoclonal antibodies, sorafenib blocks the activity of various structures within tyrosine kinase, slowing the progression of many solid tumors and of metastatic melanoma. It is administered orally, at a dose of 400 mg twice a day. However, its activity is not limited exclusively to the tumor and it is frequently associated with various adverse reactions such as hypertension, asthenia, anorexia, diarrhea, and skin disorders. More than 93% of patients on monotherapy with sorafenib will display adverse skin reactions, including alopecia (in up to 23% of cases), stomatitis (12%–35%), xerosis (11%–23%), or seborrheic dermatitis-like, erythematous, desquamative facial rashes (in up to 2% of cases).<sup>3</sup>

Cases have also been reported of subungual splinter hemorrhages, leukocytoclastic vasculitis,<sup>4</sup> exudative erythema multiforme,<sup>5</sup> and keratoacanthomas.<sup>6</sup> But the most common skin reaction with this drug is the hand-foot syndrome, which appears in up to 62% of cases.<sup>5</sup>

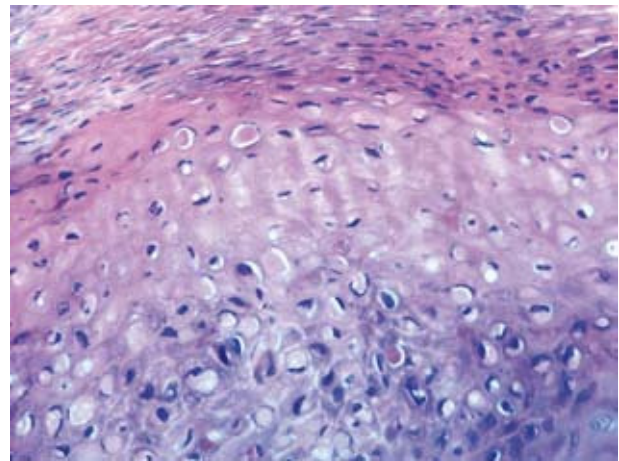
We define this syndrome as a skin reaction that is rarely painful or associated with paresthesia, is sometimes bullous, and appears in 22% to 62% of patients being treated with sorafenib.<sup>7</sup> It presents clinically as erythematous, edematous plaques associated with hyperkeratosis and desquamation in a symmetrical distribution on the palms and soles of the feet, with the occasional involvement of other sites, including the sides of the fingers and the periungual area.<sup>2</sup> The lesions tend to appear 2 to 4 weeks after starting treatment and are dose dependent, disappearing rapidly after the interruption of treatment.<sup>2</sup>

The cause is unknown, but the fact that this is a dose-dependent reaction suggests there is a direct toxic effect on keratinocytes in the skin, although these do not express vascular endothelial growth factor receptor, the target receptor of sorafenib.<sup>2</sup>

From a histological point of view, orthokeratotic hyperkeratosis is seen in the epidermis with extensive parakeratosis in the stratum corneum and marked irregular epidermal hyperplasia with focal hypergranulosis. There is significant intercellular edema with exocytosis of lymphocytes within the hyperplastic epidermis. There is moderate edema of the papillary dermis and a superficial, perivascular lymphocytic infiltrate.<sup>1</sup> Differential diagnosis principally includes palmoplantar erythrodysesthesia caused by other chemotherapy agents—such as cytarabine, fluorouracil, capecitabine, or doxorubicin—where the lesions tend to be more extensive, are associated with paraesthesia and pain, and have characteristic histological findings.<sup>8</sup> Apart from hyperkeratosis and parakeratosis of the corneal layer, spongiosis is present and apoptotic cells are observed in the epidermis, associated with vacuolar degeneration of the basal layer and a perivascular lymphocytic infiltrate in the mid dermis.<sup>9</sup>



**Figure 2.** Epidermis with thick, orthokeratotic corneal layer, an extensive underlying area of parakeratosis, and significant irregular acanthosis. Hematoxylin-eosin,  $\times 100$ .



**Figure 3.** Occasional necrotic keratinocytes with no signs of vacuolar degeneration of the basal layer. Hematoxylineosin,  $\times 400$ .

Treatment consists either of reducing drug dosage or interruption of treatment for 1 or 2 weeks.<sup>2</sup> Several studies have concluded that the appearance of skin lesions associated with the use of sorafenib could also be related to greater response to the drug, just as is the case with other chemotherapy drugs such as epidermal growth factor receptor inhibitors.<sup>10</sup> In conclusion, our patient presented edematous, hyperkeratotic, and virtually painless palmar and plantar lesions similar to those described in hand-foot syndrome, following treatment with sorafenib. The temporal relationship between administration of the drug and the appearance of the lesions, the histological study (typical although not characteristic), and improvement

of the symptoms following reduction of drug dosage confirmed the suspected diagnosis and agreed with the findings published by other authors.

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#### Conflicts of Interest

The authors declare no conflicts of interest.

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## Nodular Secondary Syphilis

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#### To the Editor:

The reduction in the number of cases of syphilis since the advent of antibiotics has diminished knowledge



**Figure 1.**  
Asymptomatic nodular lesions on the face

of the disease. However, “the great simulator” is still amongst us and we must maintain a high degree of diagnostic suspicion.<sup>1</sup> Common forms of clinical presentation are complemented by extremely rare cutaneous manifestations that complicate diagnosis, as in the case presented here.

A 58 year-old white man, with no relevant medical history, attended for an asymptomatic rash on the face and chest with onset 4 weeks previously (Figure 1). He reported no asthenia, fever, weight loss, night sweats, or other symptoms. On physical examination, the man had a healthy appearance, with multiple painless nodules of an intense pink color and firm consistency measuring approximately 1 cm in diameter located on the face and chest. There was no ulceration of the lesions. The palms, soles of the feet, and mucous membranes were unaffected. The hair and nails showed no abnormalities. There were multiple painless symmetrical adenopathies in the cervical and axillary regions, but with no sign of hepatosplenomegaly.