Sorafenib-asssociated hand-foot syndrome treated with topical calcipotriol

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INTRODUCTION

Sorafenib is a multitargeted potent antiangiogenic tyrosine kinase inhibitor.[1] Sorafenib has antiproliferative and antineoplastic effects in addition to antiangiogenic effects.[2] According to research, the use of sorafenib is effective in the treatment of advanced hepatocellular carcinoma.[3,4] However, sorafenib has several side effects including hand-foot skin reaction, alopecia, and Stevens-Johnson syndrome.[5,6]

Dermatologic side effects are the most common side effects of sorafenib, accounting for more than 10%. The most common ones are maculopapular exanthema, hand-foot syndrome, facial erythema, xerosis, and alopecia.[7] These side effects are usually mild to moderate in severity and may reduce with appropriate therapy, dose reduction, or discontinuation of sorafenib treatment.[8]

The sorafenib-associated hand-foot syndrome is characterized by symmetric painful erythematous plaques in the palmoplantar areas, which include the dorsum of hands and feet and periungal areas. Vesicles and peeling may occur in severe cases. These patients may complain of a tingling sensation, intolerance of contact with hot objects, difficulty walking, and difficulty holding objects. Histopathologic examination finds epidermal hyperplasia, nonspecific inflammatory cell infiltration, and dilate dermal veins in the dermis.[9]

The following treatment is recommended in patients with sorafenib-associated hand foot syndrome: moisturizers, topical or systemic steroids, tazarotene 0.1% cream, nicotine patch, vitamin E, pyridoxine, and cyclooxygenase inhibitor 2 for severe reactions.[10,11]

Here we present our treatment experience in a patient with grade 3 sorafenib-associated hand foot syndrome.

CASE

We present the case of a 70-year-old man with chronic hepatitis B infection for 13 years and advanced hepatocellular carcinoma for a year. This patient started using sorafenib 1 year ago because of hepatocellular carcinoma (tablets, 800 mg/d [2 × 400, mg]). In the second month of the therapy, he complained of thickening and darkening of dorsum of the hands and the feet, tingling sensation, and intolerance of contact with hot objects. On physical examination, hyperkeratosis and warty protrusions were noted on palms and dorsum of hands (Fig 1, *A* and *B*) and feet (Fig 2, *A*). There were no other lesions elsewhere on the skin or mucous membranes. In addition, there were no associated systemic symptoms. On histopathologic examination, epidermal hyperplasia, papillomatosis, and hyperkeratosis were observed (Fig 3). Clinicopathologic correlation confirmed the diagnosis as sorafenib-related hand-foot syndrome, and because it interfered with normal activities, its severity was documented as grade 3. The patient was prescribed topical calcipotriol cream, and the lesions decreased within 2 weeks of treatment without discontinuing the use of sorafenib (Fig 1, *C* and *D* and Fig 2, *B*).

DISCUSSION AND CONCLUSION

In a phase 2 study, 93% of patients with renal cell carcinoma receiving 2 doses of 400 mg/d of sorafenib had dermatologic findings including rash and

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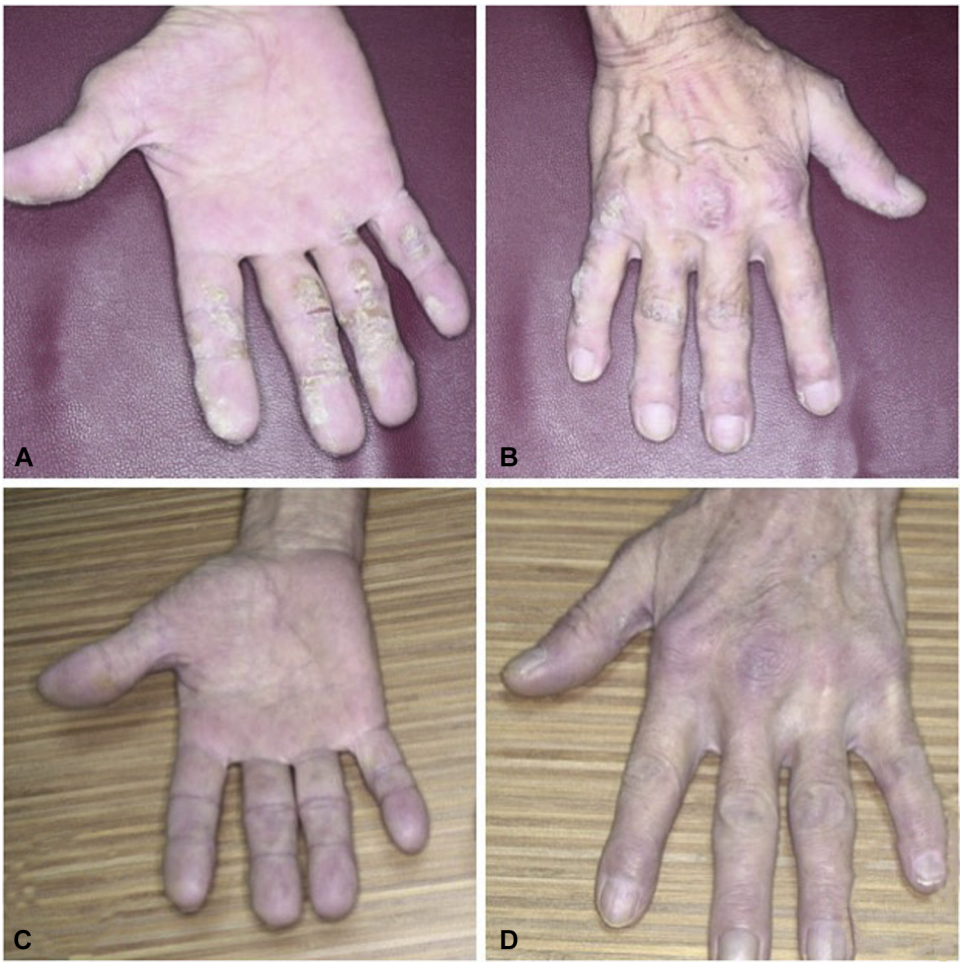

Fig 1. Sorafenib-associated hand-foot syndrome. **A** and **B**, Hyperkeratosis and warty protrusions on palms and dorsum of hands. **C** and **D**, Total disapearence of the lesions after 2 weeks.

desquamation (66%), hand-foot skin reaction (62%), and alopecia (53%).[12] Most of these symptoms were graded between 1 and 2 in severity; however, only 17% had grade 3 or 4 severity.[7] In a meta-analysis of patients using sorafenib, the frequency of hand-foot syndrome was 33%. Severe hand-foot reaction rate was found to be 8.9%.[13] Dose-dependent occurrence of the symptoms of sorafenib-associated hand-foot syndrome indicates that sorafenib is directly toxic to the skin.[14] Classical palmoplantar erythrodisesthesia seen with chemotherapeutic agents such as capecitabine may be difficult to distinguish from hand-foot syndrome induced by sorafenib.[15] Sorafenib-induced hand-foot syndrome is usually less severe and more localized and often more hyperkeratotic.[7] Classical erythrodisesthesia lesions caused by chemotherapeutics often present on less-pressure-exposed areas with diffuse lesions, whereas some patients using sorafenib may present with hyperkeratotic plaques at pressure-exposed areas only. The severity of sorafenib-associated hand-foot syndrome is determined by the National Cancer Institute Cancer Therapy Evaluation Program.[16] Treatment of grade 1 and grade 2 hand-foot syndrome is not recommended except for preventive measures and moisturizers. Topical or systemic treatments are recommended in grade 3 and grade 4 sorafenib-associated hand-foot syndrome.[16]

Patients and physicians should be aware of prevention and management of sorafenib-related hand-foot syndrome. Symptomatic treatments should given for grade 3 sorafenib-associated hand-foot syndrome. The sorafenib dose should be reduced to 400 mg/d for at least 7 days and up to 28 days in grade 2 sorafenib-associated hand-foot syndrome. If the symptoms do not disappear or reduce to grade 1, the treatment should be discontinued for at least 7 days until the severity is reduced to grade 1 or until the symptoms dissappear. After interruption of treatment, the daily sorafenib dose should be

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