Sneddon-Wilkinson Disease Induced by Sorafenib in a Patient with Advanced Hepatocellular Carcinoma

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Abstract

Sorafenib is the standard treatment for patients with advanced hepatocellular carcinoma (HCC), although it is known to cause a variety of dermatologic adverse events. Subcorneal pustular dermatosis (SCPD), also known as Sneddon-Wilkinson disease, is a rare skin eruption that accompanies various systemic disorders and may become chronically progressive. We herein describe the case of a patient who developed SCPD after sorafenib administration. The dermatologic reaction was improved by the cessation of sorafenib and worsened by its readministration. Clinicians treating HCC patients with sorafenib should be aware of the possibility of SCPD.

Key words: Sneddon-Wilkinson disease, subcorneal pustular dermatosis, advanced HCC, sorafenib

(Intern Med 54: 597-600, 2015)
(DOI: 10.2169/internalmedicine.54.3675)

Introduction

Sorafenib is an oral multitargeted tyrosine kinase inhibitor with a potent anti-angiogenic activity (1). The administration of sorafenib has been shown to be effective for treating advanced hepatocellular carcinoma (HCC) (2, 3) and has become a standard therapy for this disease (1). However, sorafenib has also been shown to cause many adverse dermatological effects, including hand-foot skin reaction (HFSR), alopecia, erythema and Steven-Johnson syndrome (4, 5).

Subcorneal pustular dermatosis (SCPD), also called Sneddon-Wilkinson disease, is a rare skin eruption characterized by the presence of flaccid pustules grouped in a circinate or striate pattern (6). The exact epidemiology and pathogenesis of this condition are unknown, although it is more common in women in the age group of 40-50 years and an association with chemoattractants, such as tumor necrosis factor (TNF)-α, has been suggested (6). Although the precise frequency is unknown, a series of case reports showed that this skin disorder is observed in patients with systemic diseases, such as IgA myeloma (7, 8), rheumatoid arthritis (9, 10), inflammatory bowel disease (11), Sjögren’s syndrome (12) and solid tumors, including lung carcinoma, apudoma and thymoma (13, 14). In particular, the occurrence of SCPD in association with both benign and malignant IgA gammopathy has been documented (7, 8, 15, 16). In contrast, SCPD is hardly recognized as a side effect of this medicine (6).

We herein describe the case of a patient with advanced HCC who developed SCPD during treatment with sorafenib and showed an improvement after sorafenib cessation. To our knowledge, this is the first description of a patient with sorafenib-induced SCPD.

Case Report

A 76-year-old Japanese man was admitted to our department for the treatment of advanced HCC. He had a history of cirrhosis due to chronic hepatitis C virus infection, as well as pneumoconiosis and mild pleural effusion, lasting for more than 10 years. However, he had no skin disorders before the administration of treatment for HCC. He had been diagnosed with HCC seven years earlier and treated periodically with radiofrequency ablation and transarterial chemoembolization (TACE). Nevertheless, the HCC had progressed, with the development of multiple nodules in...
both lobes that were refractory to TACE. The patient’s hepatic reserve and systemic organ function were good (serum total protein: 8.6 g/dL, albumin: 4.0 g/dL, aspartate aminotransferase: 49 U/L, alanine aminotransferase: 56 U/L, γ-glutamyl transpeptidase: 47 U/L, alkaline phosphatase: 326 U/L, total bilirubin: 0.6 mg/dL, blood urea nitrogen: 9 mg/dL, creatinine 0.6 mg/dL, white blood cell count: 4,620/μL, hemoglobin: 14.0 g/dL, platelet count: 12.7×10⁴/μL). He was therefore started on sorafenib (800 mg/day). Twenty days later, however, he developed grade 2/3 HFSR, and the dose of sorafenib was reduced to 400 mg/day. Computed tomography performed after a total of 60 days of treatment with sorafenib showed stable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria (17). The HFSR had also improved to grade 1, and the dose of sorafenib was increased to 600 mg/day. Ten days later, or 70 days after the initiation of sorafenib, multiple erythematous skin eruptions in a circular or linear pattern with mild itching and pain were observed on the extremities (Fig. 1A). A skin biopsy showed spongiosis, vacuolar changes and subcorneal pustular formation with neutrophil dominant infiltration in the superficial epidermis (Fig. 1B); bacterial bodies and fungi were not detected on Gram or PAS staining. Subepidermal blistering was absent. The patient was thus diagnosed with SCPD. Strong topical steroid therapy was subsequently initiated, and the dose of sorafenib was reduced to 400 mg/day. Although the SCPD showed some improvement, it persisted for approximately seven months (Fig. 1C, 2). In addition, the SCPD resolved when the sorafenib therapy was transiently discontinued due to the use of additional TACE for progressive HCC nodules; however, it again recurred when the sorafenib treatment was re-started (Fig. 2). Sorafenib was therefore permanently discontinued 12 months after the start of treatment, which resulted in the disappearance of SCPD within two or three months (Fig. 1D, E). Since that time, the patient has received hepatic arterial infusion chemotherapy with 5-fluorouracil and cisplatin.
thought to be induced by chemotactic factors, such as TNF-alpha, in the uppermost epidermis, with increased TNF-alpha concentrations in the serum and blister fluid in patients with SCPD (20). Although the precise mechanisms remain unknown, the presence of chemotactic factors associated with systemic disorders in the epidermis may induce SCPD. Our patient developed SCPD after sorafenib administration in the absence of any systemic disorders, including IgA myeloma, rheumatoid arthritis, Sjogren’s syndrome and inflammatory bowel disease. The presence of pneuomoconiosis, a type of chronic pleural inflammation, and/or liver cirrhosis, a type of chronic hepatic inflammation, in our advanced HCC patient may have been associated with the onset of SCPD via the migration of neutrophils to the epidermis. A recent case report described the onset of pustular eruptions induced by sorafenib in a patient with HCC, liver cirrhosis and psoriasis vulgaris (22). In that patient, the pustules were thought to be associated with the exacerbation of psoriasis, as they appeared only on pre-existing psoriatic plaques (22). In addition, SCPD was noted at the injection site of recombinant human granulocyte-macrophage colony-stimulating factor in a patient with IgA myeloma (8). Sorafenib inhibits a number of tyrosine kinases, including the vascular endothelial growth factor receptor family, platelet-derived growth factor receptor and RAF kinase (1). Sorafenib-induced HFSR has also been suggested to be caused by drug leakage from capillaries damaged by subclinical trauma (23). The administration of sorafenib may be associated with the formation of pustules via the actions of chemotactic factors induced by drug leakage from capillaries due to underlying hyperglobulinemia as a result of cirrhosis and chronic inflammation.

In conclusion, the administration of sorafenib may be associated with the development and progression of SCPD, as well as various other skin disorders. Skin biopsies are required to make an accurate diagnosis, and dose reduction of sorafenib and the administration of topical steroids may enable the continuation of sorafenib treatment. Clinicians treating patients with anti-angiogenic agents, including sorafenib, should thus be aware of the possibility of SCPD as well as other adverse cutaneous effects.

The authors state that they have no Conflict of Interest (COI).

Discussion

Sorafenib is a multikinase inhibitor approved for the treatment of unresectable HCC and advanced renal cell carcinoma (RCC) in Japan. HFSR is frequently observed during the use of sorafenib in patients with RCC, including 21.0% of the patients in the global phase III SHARP trial (2) and 45.0% of the patients in the phase III Asia-Pacific trial (3). Furthermore, adverse dermatological events have been reported in 80.2% of sorafenib-treated patients with advanced RCC, with HFSR occurring in 55.0% of patients assessed in a phase 2 trial in Japan (18). Furthermore, a retrospective study in Korea showed that adverse cutaneous events are frequently noted in patients treated with sorafenib (81/109, 74.3%) and sunitinib (96/119, 80.7%) (4), highlighting the importance of managing adverse skin events during treatment with multitargeted kinase inhibitors with a potent anti-angiogenic activity, such as sorafenib, especially in Asian patients.

SCPD is a rare chronic pustular eruption that accompanies various systemic disorders, such as autoimmune diseases and malignancies. SCPD is characterized by the presence of sterile pustular eruptions caused by neutrophil migration through the epidermis and aggregation beneath the stratum corneum (19). This hyperactivation of neutrophils is thought to be induced by chemotactic factors, such as TNF-alpha, in the uppermost epidermis, with increased TNF-alpha concentrations in the serum and blister fluid in patients with SCPD (20). In addition, interleukin-8 and C5a concentrations above the normal levels have been observed in the scale extracts of patients with SCPD (21). Although the precise mechanisms remain unknown, the presence of chemotactic factors associated with systemic disorders in the epidermis may induce SCPD. Our patient developed SCPD after sorafenib administration in the absence of any systemic disorders, including IgA myeloma, rheumatoid arthritis, Sjogren’s syndrome and inflammatory bowel disease. The presence of pneuomoconiosis, a type of chronic pleural inflammation, and/or liver cirrhosis, a type of chronic hepatic inflammation, in our advanced HCC patient may have been associated with the onset of SCPD via the migration of neutrophils to the epidermis. A recent case report described the onset of pustular eruptions induced by sorafenib in a patient with HCC, liver cirrhosis and psoriasis vulgaris (22). In that patient, the pustules were thought to be associated with the exacerbation of psoriasis, as they appeared only on pre-existing psoriatic plaques (22). In addition, SCPD was noted at the injection site of recombinant human granulocyte-macrophage colony-stimulating factor in a patient with IgA myeloma (8). Sorafenib inhibits a number of tyrosine kinases, including the vascular endothelial growth factor receptor family, platelet-derived growth factor receptor and RAF kinase (1). Sorafenib-induced HFSR has also been suggested to be caused by drug leakage from capillaries damaged by subclinical trauma (23). The administration of sorafenib may be associated with the formation of pustules via the actions of chemotactic factors induced by drug leakage from capillaries due to underlying hyperglobulinemia as a result of cirrhosis and chronic inflammation.

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