Sorafenib-induced Pemphigus Vulgaris

Ajay Deshpande
Department of Dermatology, Maharashtra Medical Foundation, Joshi Hospital, Pune, Maharashtra, India

Address for correspondence: Dr. Ajay Deshpande, Maharashtra Medical Foundation, Joshi Hospital, 777, Shivaji Nagar, Pune - 411 004, Maharashtra, India. E-Mail: deshpandesajay.68@gmail.com

ABSTRACT
Sorafenib is a tyrosine kinase inhibitor approved for the treatment of primary kidney cancer, advanced primary hepatocellular carcinoma, and radioactive iodine-resistant advanced thyroid carcinoma. Sorafenib is known to cause milder cutaneous side effects such as maculopapular rash and serious cutaneous drug reactions such as desquamation of the skin, hand-foot syndrome, Stevens-Johnsons syndrome and toxic epidermal necrolysis. We report a histopathologically proved case of pemphigus vulgaris caused by sorafenib.

Key Words: Drug-induced pemphigus, sorafenib, tyrosine kinase inhibitor

INTRODUCTION
Sorafenib is a tyrosine kinase inhibitor approved for the treatment of primary kidney cancer, advanced primary hepatocellular carcinoma,[1] and radioactive iodine-resistant, advanced thyroid carcinoma. Sorafenib is known to cause milder cutaneous side effects such as maculopapular rash and serious cutaneous drug reactions such as desquamation of the skin, hand-foot syndrome, Stevens-Johnsons syndrome, and toxic epidermal necrolysis. Although drug-induced pemphigus is commonly reported due to thiol drugs such as angiotensin-converting enzyme inhibitors, d-penicillamine, captopril, pyritinol, piroxicam, thiopronin, and nonthiol drugs such as aminopenicillins, rifampicin, and propranolol,[2] drug-induced pemphigus due to sorafenib is not reported in literature to the best of our knowledge. We report a case of a 70-year-old male patient on sorafenib therapy developing sorafenib-induced pemphigus vulgaris.

CASE REPORT
A 70-year-old male, a known case of hepatoma with liver cirrhosis, came with chief complaints of pruritic lesions over both legs of of two months duration. Lesions started with burning sensation followed by fluid-filled, tiny blisters which ruptured to give rise to large denuded areas on an erythematous base. He was on tablet sorafenib once a day since the last six months for his hepatoma. The patient was nondiabetic and was normotensive.

His general examination was otherwise within normal limits except for pallor. His hemogram revealed anemia and raised liver enzymes. X-ray chest was normal and sonography of abdomen showed cirrhotic changes of liver and hepatoma. Dermatological examination showed large denuded areas covered with crusts on an erythematous base involving back of thigh and calf [Figure 1]. Nikolsky’s sign was negative. Oral and genital mucosae were normal.

Skin biopsy from on the margin of the erosions showed suprabasal clefting with acantholytic cells. Basal layer keratinocytes were intact giving rise of “row of tombstone” like appearance which was suggestive of pemphigus vulgaris [Figure 2]. The patient was given symptomatic treatment and was advised to discontinue sorafenib. On follow-up after two weeks, all his lesions had healed with postinflammatory hyperpigmentation [Figure 3].

To confirm our diagnosis of sorafenib-induced pemphigus vulgaris, a re-challenge of sorafenib was given for 7 days and lesions recurred [Figure 4].

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DISCUSSION

Sorafenib is a kinase inhibitor approved for the treatment of primary kidney cancer, advanced primary hepatocellular cancer, and radioactive iodine-resistant, advanced thyroid carcinoma. It is still the only systemic drug approved for advanced hepatocellular carcinoma.[1]

Dermatological adverse effects such as desquamation of the skin, hand-foot skin reaction, xerosis, Stevens–Johnson syndrome, and even toxic epidermal necrolysis have been reported due to sorafenib. Of these, hand-foot syndrome and maculopapular rash[3] are the most commonly reported cutaneous side effects of sorafenib. In the Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol trial, hand-foot syndrome occurred in 21% of enrolled patients.[4]

A severe alopecia due to sorafenib increases during the therapy. Common systemic side effects of sorafenib include diarrhea, arterial hypertension, and fatigue.[5,6]

Exact mechanism of action of cutaneous or systemic side effects due to sorafenib is not known. However, it is suggested that side effects of sorafenib could be because of inhibition of one or more drug targets, such as the vascular endothelial growth factor receptor-1, 2, 3 family, platelet-derived growth factor receptor family, stem-cell growth factor receptor (c-KIT), Fms-like tyrosine kinase 3, the receptor encoded by the Ret proto-oncogene, and Raf serine/threonine kinase activity in normal organs.[7]

Drug-induced pemphigus vulgaris is a well-known variant of pemphigus vulgaris, d-penicillamine and captopril being the most common thiol-containing drugs responsible for drug-induced or drug-triggered pemphigus. Mechanism of thiol drug-induced pemphigus is biochemical acantholysis of keratinocytes without formation of anti-desmoglein antibodies.[2] On review of literature, there are no reports of sorafenib causing pemphigus vulgaris. Average time

Figure 1: Erosions after starting therapy.

Figure 2: Suprabasal clefting and intact basal keratinocytes suggestive of pemphigus vulgaris (H and E, ×40).

Figure 3: Healing of skin erosions after stoppage of the drug.

Figure 4: Recurrence of flaccid blisters and erosions after restarting the drug.
period for the development of drug-induced pemphigus due to thiol drugs is 11 months while that due to nonthiol drugs is 4 months.[8] Our patient was on sorafenib since the last 6 months. Pemphigus triggered by nonthiol drugs regress spontaneously in 15% patients after stopping the drug. In our case, patient recovered within 2 weeks after cessation of sorafenib. Morphological and histologic presentation of pemphigus in our patient resembles that of drug-induced pemphigus due to nonthiol-containing drugs.

This is the first report of pemphigus vulgaris caused by sorafenib. In this case, the histopathological changes of involved skin, healing of skin lesions on discontinuation of sorafenib without any treatment, and reappearance of similar skin lesions on re-challenging with offending drug (sorafenib) definitively helps to prove pemphigus vulgaris as one of the adverse effects of sorafenib.

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**Conflicts of interest**
There are no conflicts of interest.

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