

Sorafenib-induced severe urticaria in a patient with hepatocellular cancer

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Abstract

Sorafenib which is used in the treatment of renal, thyroid and hepatocellular cancers is a multi-targeted tyrosine kinase inhibitor. Though sorafenib is associated with some side effects, it is known that sorafenib is generally well tolerated compared to other tyrosine kinase inhibitors. In the present case, hepatocellular cancer was diagnosed seven months ago. The disease was in stage IIIB at the time of diagnosis. Sorafenib was initiated with a dose of 400 mg twice daily because of disease progression after two cycles of doxorubicin. The reactions on the skin of the arms and the body of the patient occurred in the eighth week of treatment. Skin biopsy was performed and urticaria was diagnosed after pathologic examination. No other disorders or drugs which may cause urticaria were detected in the patient. Skin reactions disappeared one week after sorafenib discontinuation without any further intervention.

Keywords

Sorafenib, urticaria, skin toxicity, antiangiogenic agent

Introduction

Sorafenib is a multi-targeted orally active small molecule tyrosine kinase inhibitor (TKI) that inhibits Raf kinase and the vascular endothelial growth factor receptor (VEGFR) intracellular kinase pathway.¹ Several side effects related to sorafenib such as hypertension, arterial thromboembolism, bleeding, cardiotoxicity, thyroid dysfunction, toxic/metabolic encephalopathy, muscle wasting, cutaneous, hepatic and renal toxicities were reported.^{2–4} The fact is that sorafenib-induced skin rash has been widely described in relation to its use in advanced renal, thyroid cancer and hepatocellular cancers.⁵ In the presented case, we aimed to report a case of reversible severe urticaria related to the use of sorafenib.

Case report

A 65-year-old man was diagnosed with hepatocellular cancer (HCC) seven months ago. The patient had no metastases at the time of diagnosis. He has previously received doxorubicin-based chemotherapy. After two cycles of chemotherapy, due to disease progression,

sorafenib was offered to the patient. The drug was prescribed for oral intake as 400 mg twice a day. The patient was admitted to hospital with complaints of skin lesions on his arm and body in the eighth week of treatment (Figure 1). The lesions were papular erythematous, itchy and painless particularly on the legs. There were vesicular eruptions at the edge of erythematous area. The oral mucosa of the patient was normal. He reported no other symptoms. On examination, there was no abnormality except for skin rash. Blood pressure was normal. The white blood cell count, hemoglobin concentration and platelet count were 7500/mm³,

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Figure 1. Skin lesions.

8.8 g/dl, and $502.000/\text{mm}^3$, respectively. The other laboratory parameters were also normal. The patient was consulted by the dermatologist. On July 2014, the intake of sorafenib was stopped and skin biopsy was performed. Topical and oral antihistaminic agents were suggested. Biopsy sample was consistent with urticaria (Figure 2). The cellular infiltrate in urticaria is usually mild and perivascular in location. There is mild dermal edema and perivascular inflammatory infiltrate composed of lymphocytes, mast cells and eosinophils. Interstitial eosinophils are also present. A week after stopping the medication, the patient was admitted again. Lesions healed up to 80% (Figure 3). After healing of lesions, sorafenib was restarted with a lower dose of 200 mg daily. When sorafenib was increased to the dose of 200 mg twice daily, we observed that skin rashes began to appear slightly again. Therefore, sorafenib was continued with the dose of 200 mg daily.

Discussion

In the era of molecularly targeted therapy, the promising survival results are observed in different tumor types. Unfortunately, the different toxicities of targeted agents limit the optimal use of them.

Sorafenib is an antiangiogenic TKI agent similar to sunitinib, axitinib, pazopanib, tivozanib, cabozantinib and cediranib. Cutaneous toxicities are especially commonly seen in the treatment with these TKI agents. Hand-and-foot skin reaction (HFSR), alopecia, stomatitis, skin discoloration, subungual splinter hemorrhage, facial and scalp erythema, xerosis and Stevens–Johnson syndrome were reported as cutaneous toxicity related to sorafenib and sunitinib.^{6,7} HFSR was more frequently reported in literature.^{6–9}

In our case, we examined grade 3 cutaneous rash (itchy, severe and generalized papular erythematous rash with vesicular eruption at the edge of

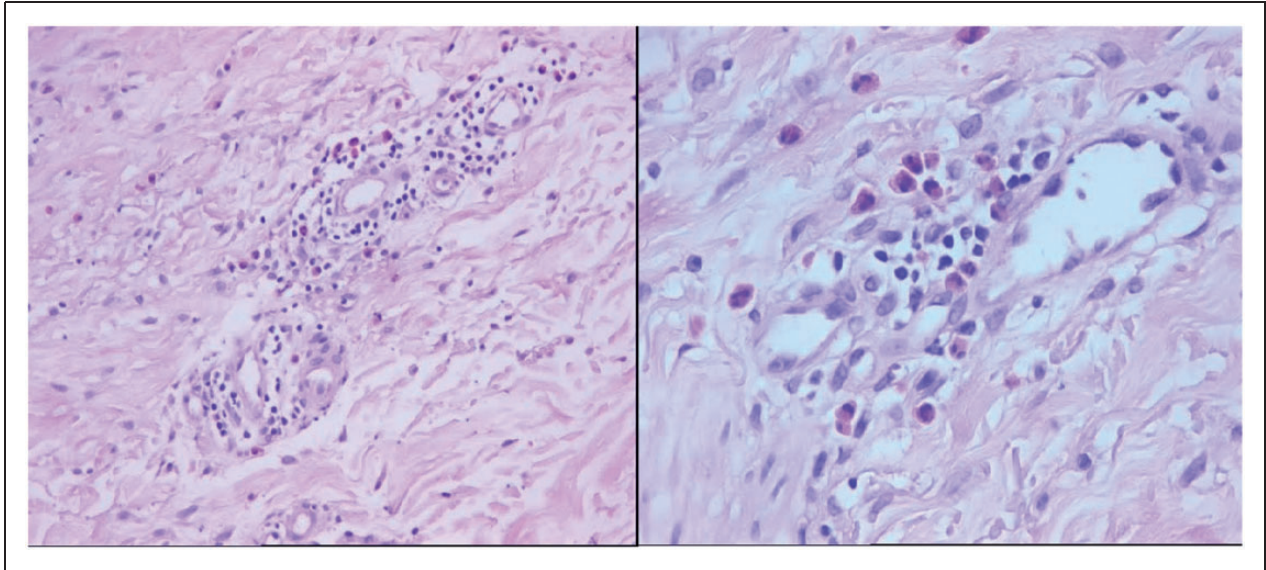


Figure 2. Pathologic imaging.



Figure 3. After the discontinuation of sorafenib.

erythematous area) according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0. Due to dissemination and severity of lesions, we thought that the discontinuation of sorafenib will be an appropriate approach. After the discontinuation of treatment with sorafenib, the itchiness

decreased, vesicles disappeared and crusts occurred in the middle of the lesions and the lesions healed completely in follow-up. The evaluation of the skin biopsy has shown no vasculitis (inflammation of blood vessels). Urticaria was reported by the pathologist.

Dermatological manifestations including rash and desquamation related to sorafenib were reported at the rate of 29%.⁸ Additionally, in a meta-analysis including 24 trials, it was reported that the incidence of all-grade rash/desquamation, HFSR, alopecia, pruritis and dry skin were found in 15–80%, 21–93%, 4–57%, 4–32% and 6–37% of cases, respectively, in patients to whom sorafenib was assigned.¹⁰ However, papular urticaria and generalized urticaria were reported at the rates of 0.01% and 0.03% in patients taking sorafenib.¹¹ There is little information about etiology. It was mentioned in literature that sorafenib had a direct inhibitory effect on the mitogen-activated protein kinase (MAP-kinase) pathway. This effect may play a role in the development of the skin toxicity.⁸ Additionally, Vascular endothelial growth factor 4 (VEGF) which was detected in normal human epidermal keratinocytes (NHEKs), and stimulating the proliferation of NHEKs is an important factor for wound repair and VEGF has a proliferative signal to NHEKs.¹² Sorafenib has an inhibitory effect against VEGFR and this effect may be responsible for skin toxicity.

In the presented case, we determined reversible severe urticaria related to sorafenib treatment in a patient with HCC. After discontinuation of the treatment with systemic and topical antihistamines, the toxicity caused by the treatment rapidly decreased. In our case, skin biopsy was performed which is an invasive procedure. The skin toxicity related to TKI agents

is quite common. Since rapid improvement was seen after discontinuation of the TKI agents no invasive procedure may be needed.

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Conflict of interest

None declared.

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