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Erythema multiforme major induced by sunitinib for metastatic renal cell carcinoma

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ABSTRACT

There are currently several options for tyrosine kinase inhibitor as a systemic therapy for metastatic renal cell carcinoma (mRCC). The successful control of adverse events caused by such drugs, along with eliciting long-term maximum effect, are the major issues with respect to the treatment strategy for mRCC. We herein report the clinical course of mRCC, in which erythema multiforme major was observed on the 13th day of the first course of sunitinib, but the symptoms improved after the immediate withdrawal of sunitinib, as well as the administration of topical steroids and oral antihistamines alone.

Introduction

Sunitinib is a multi-targeted tyrosine kinase inhibitor (mTKI) which is recommended for unresectable or metastatic renal cell carcinoma (mRCC) treatment. It is suggested that continuing the administration of sunitinib, while successfully managing adverse events, may play a more important role as a strategic first line therapy for mRCC going forward. Hand-foot syndrome is a frequent skin toxicity that appears in the dose dependence of sunitinib. On the other hand, the expression of erythema multiforme major (EM major) is rare and may possibly transition to Stevens-Johnson syndrome (SJS) with a high mortality rate, or toxic epidermal necrolysis (TEN), making early treatment intervention and cause identification very important.[1,2]

Case presentation

A 75-year-old woman visited the Urology Department as an outpatient, with chief complaints of right abdominal pain, gross hematuria, and malaise. She only had a past medical history of hypertension. Based on the results of contrast CT, we found a right renal tumor with a diameter of 93 mm which exhibited tumor development in the right renal vein and metastasis to the lungs and para-vena lymph node and mesenteric lymph node, with a clinical stage of T3aN2M1. She did not desire immediate surgical intervention and upon signing the informed consent, regarding the risk benefit for prior systemic treatment with molecular targeted drugs, she initiated daily administration of Sunitinib 50 mg following a standard 4 weeks on/2 weeks off schedule. Thirteen days after the initiation of treatment, she complained of an eating disorder due to the development of an oral ulcer, accompanied by erythema spreading throughout her entire body, with an itching sensation, and general malaise, which thus resulted in her visiting our institution. Her blood pressure diary indicated her course was at the maximum of 146/73. Oval erythemas of approximately 10–20 mm and erythemas showing the target lesion were found on the abdomen, back, limbs, and face, while partially enlarged erythemas on the back had merged to form a geographic site (Fig. 1). Ulcer of the outer tongue and erosion of the oral cavity mucosa were observed, while the itching sensation was mainly found from the back of the hand to the forearm, along with the trunk. ALP increased to 993 U/L, while AST and ALT increased to 127 U/L and 179 U/L, respectively, in blood tests. She was hospitalized the same day and sunitinib administration was withdrawn, after which we subsequently performed nutritional replacement from the peripheral vein and administered hepatoprotective drugs, in addition to applying topical steroids and orally administering antihistamines for erythema. A punch biopsy of erythema and a Lymphocyte Transformation Test (LTT) were conducted on the 2nd day of sunitinib withdrawal. Although LTT of Sunitinib was negative, it was a non-contradictory finding in the skin biopsy tissue images, as a drug eruption (Fig. 2). It was diagnosed as sunitinib-induced EM major, due to a lack of any history of infectious diseases or herpes virus in blood tests, as well as based on the clinical course and histopathological diagnosis. EM in the face and abdomen showed a tendency to improve on

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Abbreviation

CT	computed tomography
EM major	erythema multiforme major
mRCC	metastatic renal cell carcinoma
mTKI	multi-targeted tyrosine kinase inhibitor
SJS	Stevens-Johnson syndrome
TEN	toxic epidermal necrolysis

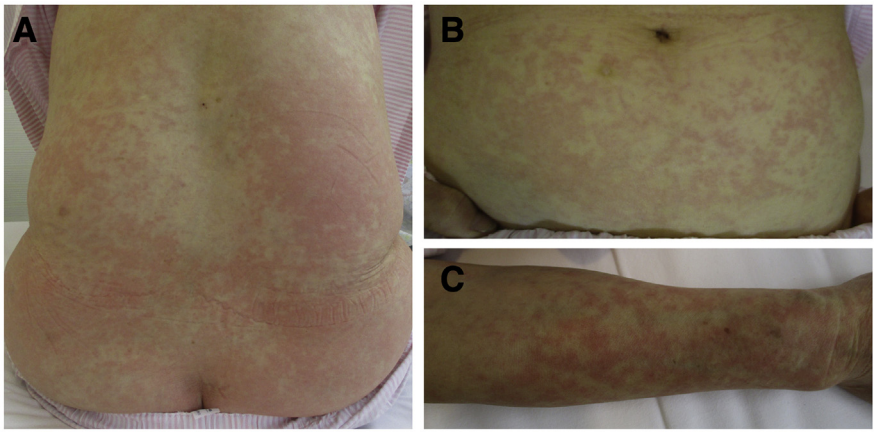

Fig. 1. (A) Depicts the back, (B) the abdomen, and (C) the skin findings of erythema multiforme seen in the right forearm.

the 5th day of sunitinib withdrawal and almost all erythemas of the limbs and back disappeared on the 7th day of withdrawal, showing improved liver function upon blood testing. Although no full improvement was found in the tongue findings, she was able to consume normal amounts at meals and was discharged on the 8th day of drug withdrawal. CT performed on the 7th day of sunitinib withdrawal confirmed a reduction in the size of both the para-vena lymph node and mesenteric lymph node.

Discussion

EM type drug eruption is a phenotype of a drug eruption caused by various drugs, such as penicillin and cephem antibiotics, antifungal drugs, antiepileptic drugs, antiinflammatory analgesics and so the like.

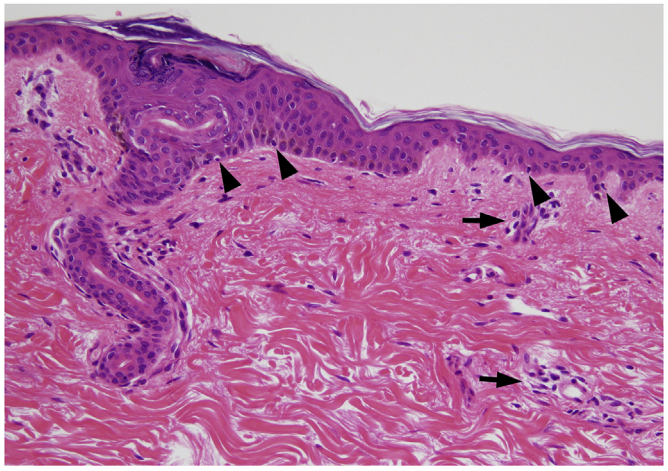

Fig. 2. Histopathological findings of a skin biopsy. Vacuolar degeneration and lymphocyte infiltration are seen at the dermis epidermal border, which is a finding of interface dermatitis (arrow head). Perivascular lymphocyte infiltration of the upper layer of dermis is a finding of perivascular dermatitis (arrow). Both are non-contradictory findings of drug eruption.

EM minor includes erythemas symmetrically on the distal extremities, whereas with EM major, eruptions, including relatively large erythemas, spread throughout the body and mild mucosal lesions in the oral cavity and ocular conjunctiva are observed as characteristics thereof. Drug eruptions caused by drugs other than antiepileptic drugs are characterized in that onset is often from day 4 to day 21 of administration, with symmetrical and broadly reddish mottled or hill-like erythemas spreading to the limbs and trunk.[3] As a method of identifying the responsible drug, patch tests and LTT are not standardized and drug induction tests are not recommended.[3] The appearance of fever, mucous membrane symptoms, blisters, and fatigue in drug eruption patients, is a finding suggesting severe disease to SJS/TEN, etc., to which attention should be paid.[3] Similar to Sunitinib, Sorafenib as mTKI is also routinely administered for mRCC. EM was reported to not be expressed, even following the re-administration of Sorafenib after stopping Sorafenib,[4] but there was also a case of positive patch tests.[5] Therefore, with respect to the mechanism of Sorafenib-induced EM expression, the involvement of nonallergic mechanisms and allergic mechanisms are taken into consideration. Sorafenib-induced EM is recognized as a skin toxicity with a frequency expression that is not rare, and at the same time, it is pointed out that it may become a surrogate marker concerning therapeutic effects.[5] On the other hand, two cases have been reported as of yet on sunitinib-induced EM major.[1,2] The timing of the expression of EM in these report cases was within 2 weeks after the initiation of treatment with Sunitinib, with no description concerning patch testing or LTT and one case shifting to SJS. In case of suspected Sunitinib-induced EM major, it is considered better to carefully examine the possibility of severity, upon hospitalization and immediate withdrawal, based on the physical findings.

Conflicts of interest

We have no conflict of interest to disclose.

Consent

Written informed consent was obtained from the patient for publication of this case report.

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None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://

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