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Case Report

Sunitinib-induced hand-foot syndrome in a Kashmiri male

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Abstract Sunitinib belongs to multiple tyrosine kinase inhibitor class of novel targeted therapies used for metastatic solid tumours including renal cell carcinoma. A variety of systemic, as well as, cutaneous side effects due to sunitinib have been described including the hand foot syndrome. We report sunitinib-induced hand foot syndrome in a 65-year-old Kashmiri male and review the literature.

Key words
Sunitinib; tyrosine kinase inhibitor; renal cell carcinoma; hand-foot syndrome.

Introduction

Hand-foot syndrome (HFS), also called hand-foot skin reaction, is a dose-limiting cutaneous toxicity of many chemotherapeutic agents.[1] Recently, the multiple tyrosine kinase inhibitor class of novel targeted therapies, including sorafenib and sunitinib, has emerged as an important cause of HFS.[2] Sunitinib was approved by the US Food and Drug Administration in 2006 for treatment of advanced renal cell carcinoma and gastrointestinal stromal tumor.[3] We report a case of sunitinib-induced hand-foot syndrome in a Kashmiri patient suffering from renal cell carcinoma.

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Case Report

A 65-year-old adult Kashmiri male, retired government employee, nonsmoker, normotensive, with type 2 diabetes mellitus on insulin for last two years, was diagnosed as metastatic left renal cell carcinoma of clear cell type in March 2012 in the medical oncology department of our tertiary care level hospital. He had presented with left flank pain and hematuria of 1 month duration prior to the diagnosis.

On evaluation, he was found to have large left renal mass with para-aortic lymphadenopathy and bilateral lung metastasis. CT guided biopsy of left renal mass revealed metastatic renal cell carcinoma of clear cell type. He was started on tyrosine kinase inhibitor, sunitinib, 50mg OD for 4 weeks/2 week off schedule in May 2012. Towards the end of first cycle, he started with multiple erythematous blisters on hands and feet, which subsided after he stopped the drug at 4

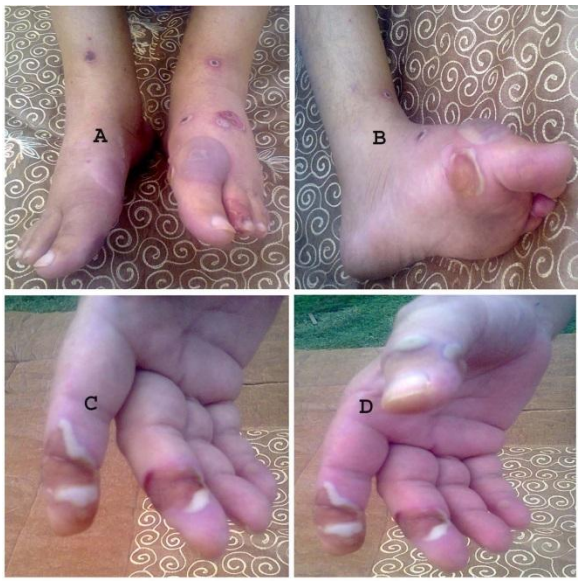

Figure 1 Well defined bullae with surrounding erythema on pressure bearing sites of hands and feet; few healing with callus formation.

weeks. At the 2nd week of 2nd cycle he again started with similar lesions on hands and feet. Dermatological consultation was sought. On dermatological examination, there were multiple, bilateral, well defined bullae with surrounding erythema confined to pressure bearing sites of hands and feet. Few lesions had central necrosis. Some of the bullae had ruptured and were in the process of callus formation (**Figure 1**). There was no involvement of mucus membranes and rest of the body. Patient was diagnosed as sunitinib-induced hand-foot syndrome. The dose of sunitinib was decreased to 37.5mg and further to 25 mg, but skin lesions did not improve and impaired his daily activity and quality of life. The drug was stopped at 3rd week and skin lesions improved and healed, some with callus formation. It was decided to consider some alternative therapy, in view of the nature of disease he was suffering from. He was put on parenteral temsirolimus 25mg IV weekly and so far had received 9 weeks of treatment and was doing well. His disease had shown partial response as documented by PET–CT after 8 weeks of temsirolimus.

Discussion

Hand-foot syndrome (HFS), also called hand-foot skin reaction, palmar-plantar erythrodysesthesia, acral erythema, Burgdorf reaction, is a dose limiting cutaneous toxicity of many chemotherapeutic agents.[1] Hand-foot syndrome was first reported in association with chemotherapy by Zuehlke in 1974.[4]

The exact pathogenetic mechanism for HFS is not known, but the most commonly accepted one is the direct toxic effect on epidermal cells.[5]

The symptoms can occur anywhere between days to months after administration of the offending medication, depending on the dose and speed of administration.[6] The patient first experiences tingling and/or numbness and further develops painful, symmetric and well-demarcated blisters, callus formation and erythematous plaques on areas of palms and soles subjected to pressure or friction. Patients may also experience severe dry skin, cracking and desquamation. The severity of the painful calluses can interfere with the patient's ability to maintain their normal schedule of activities and lead to a decline in function and quality of life.[7]

HFS invariably recurs with resumption of chemotherapy and symptoms usually resolve 1-2 weeks after cessation of chemotherapy.[7,8]

Multiple tyrosine kinase inhibitor class of novel targeted therapies, including sorafenib and sunitinib, has emerged as an important cause of HFS[2]. Sunitinib is an oral multi-targeted tyrosine kinase inhibitor that targets VEGFR (1-3), PDGFR-α, c-KIT, FLT-3, colony-stimulating factor receptor 1, and the glial cell-line-derived neurotrophic factor receptor.[9] Despite their higher specificity when compared with standard chemotherapy, the activity of these agents is not

limited to tumor cells and a variety of systemic and cutaneous adverse side effects have been reported. Most notable cutaneous toxic effects include mucositis, rash, alopecia, xerosis, xerostomia and hand-foot skin reaction (HFSR).[9]

The main treatment for HFS is discontinuation of the offending drug and symptomatic treatment to provide analgesia, decrease edema, provide wound care, and prevent superinfection and also corticosteroids use. However, the treatment for the underlying cancer of patient must not be neglected. Often, the discontinued drug can be substituted with another cancer drug or cancer treatment.[10]

Our patient had typical clinical presentation of sunitinib-induced HFS, showing direct temporal association. The drug was subsequently replaced with temsirolimus, leading to complete clinical cure of hand foot syndrome without relapse.

Conclusion

Cutaneous adverse side effects including hand-foot syndrome caused by various chemotherapeutic agents, including the relatively specific tyrosine kinase inhibitors like sunitinib should be recognized early and managed aggressively, as it is associated with decline in function and quality of life in already disturbed cancer victim. This will help in deciding whether to continue with the same drug or change to some alternative.

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