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Unexpected skin lesions after axitinib treatment

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1. Introduction

After the age of cytotoxic treatment, new era of biological agent have been started in oncology. These biological agents are composed of immunomodulators, monoclonal antibodies, and tyrosine kinase inhibitors (TKI). Among them, TKIs target important intracellular pathways to prevent tumour development and metastases. Though, these agents are more specific to the cancer cells compared to the cytotoxic chemotherapeutics, they have class side effects like diarrhea, mucositis, and skin toxicities. Hand foot skin reaction (HFSR) is the most reported skin toxicity. Its rate changes with the offending TKI and can be seen around 30% of the patients. Exact pathogenesis is not clear.

Axitinib, new TKI agent, is approved at the first and second line therapy in advanced renal cell cancer (RCC)[1,2]. It is more specific to vascular endothelial growth receptor (VEGF) pathway compared to sunitinib, sorafenib and pazopanib, and less toxic in respect of skin toxicities.

We report a patient in whom a particular skin eruptions resulted from axitinib (20 mg/day) at the 5th month of the treatment. To the best of our knowledge, no similar accounts have this type location and timed skin lesions reported in literature.

2. Case

A 58-year-old man presented with a two week history of a skin eruptions and grade 2 stomatitis. He had history of coronary artery disease with ejection fraction of 50% in 2012. Three years before admission he had nephrectomy for clear cell carcinoma of the kidney. At initial diagnosis, tumor stage was stage 2 (T2N0M0). In October 2013, multiple lung metastases were developed and treatment with pazopanib at a dose of 800 mg/day was started. In July 2014, disease progression with progressive lung metastases, new occurrence of subcutaneous nodules and cranial lesions was shown. First, he had treated with whole brain radiotherapy then treatment with axitinib (2 × 5 mg/day—>2 × 10 mg/day at 14th day) was started. During treatment period, the patient experienced grade 1 diarrhea and stomatitis however blood pressure (most feared complication of axitinib) was normal. Radiological response evaluation in November 2014, revealed partial response to treatment.

The patient's recent drug history was negative other than routine medication that has been used for a long period. Skin lesions were characterized by discrete, well-demarcated, coin-shaped, and thick crusted erosions accompanied by pruritus (Fig. 1a, 1b, 1c, 1d, 1e). Histopathological examination of incisional biopsy revealed epidermal necrosis and eosinophil-rich inflammation in dermis (Fig. 2). Pathological evaluation for potential infectious agents were negative. Immunohistochemical evaluation ruled out the immune process with negative staining for antigen-antibody complex. Furthermore, the patient was diagnosed as fixed drug eruption with axitinib. After consultation with department of the dermatology, 1 mg/kg methyl prednisolone with IV route was started and offending drug 'axitinib' was suspended. After this manipulation, patient's skin eruptions resolved significantly. On the 10th day of admission, the patient had symptoms of progressive dyspnea, radiologic evaluation was negative for pulmonary emboli, pneumonia and, progressive primary disease. Cardiac failure with left ventricular dysfunction was developed and this diagnosis was consistent with physical examination and findings of echocardiography. The patient lost on the 17th day of admission with progressive cardiac failure.

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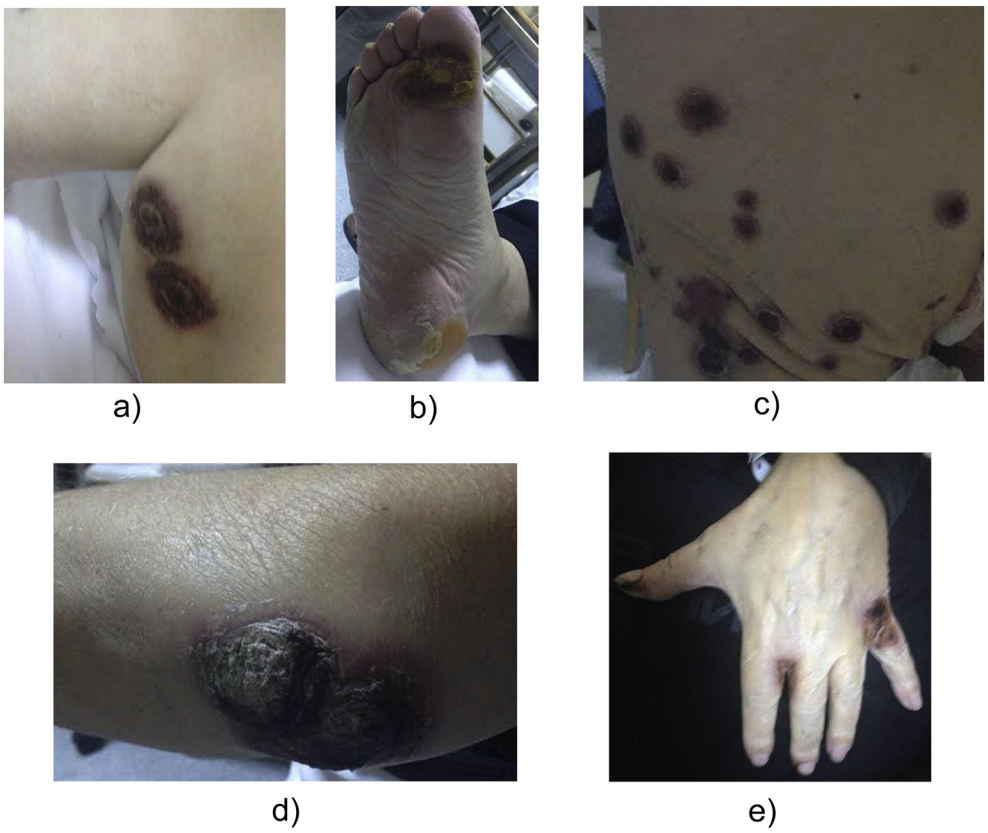

Fig. 1. 1a,1b,1c,1d,1e: Skin lesions were characterized by discrete, well-demarcated, coin-shaped, and thick crusted erosions accompanied by pruritus.

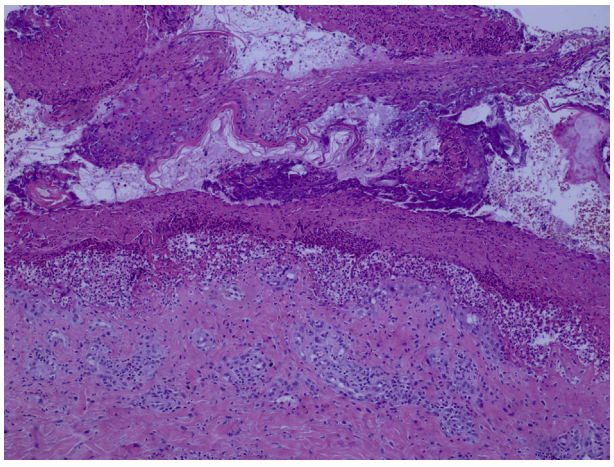

Fig. 2. Epidermal necrosis and eosinophil-rich inflammation in dermis.

3. Discussion

After the exploration of different intra cellular pathways'importance in cancer development, we have experiencing treatment paradigm shift from classic cytotoxic drugs to the biological agents that target these pathways in the field of oncology.[3] This novel therapies have been also changed treatment algorithm of the advanced kidney cancer and is resulted with significant improvement of survival outcomes.[4]

Among them, Axitinib is a strong inhibitor of the VEGF pathway. Axitinib was approved by the FDA at the first and second line treatment for the treatment of advanced RCC[2,5] since 2011. Even though, in vitro study of axitinib failed to show its activity on PDGFRs, B-raf, c-kit, and Flt-3, studies with axitinib reported rate of all grade HFSR, most common form of skin reaction, was around 30%.[3] Therefore, the authors suggested that axitinib has some in-vivo activity on these pathways addition to VEGF pathway, which are believed to be responsible from HFSR as well as other cutaneous drug reaction. HFSR is characterized by palmoplantar lesions in areas of friction like as hands and feet. HFSR is appeared during the 3rd and 4th week of treatment and histopathological evaluation is characterized by dermal vascular modifications, scattered keratinocyte necrosis, and intra-epidermal cleavage, which may be mediated via direct anti-VEGFR and/or PDGF receptor effects on dermal endothelial cells.[6] Although, HFSR is the most common skin reaction, stomatitis and oral mucosal lesions, alopecia, hair depigmentation, facial erythema resembling seborrheic dermatitis, finger changes with subungual splinter hemorrhages, and yellow skin pigmentation are reported in literature.[7] Most of these different types of skin reactions present during the first 2 months of therapy and pathologic mechanism of these reactions is not clearly understand.

In present case, skin eruptions developed in the 5thmonth (expected time for the skin eruption after 2–6 weeks) of the axitinib treatment at the extensor surface of the buttocks and elbows, and, also at the hands and feet. Furthermore, both site and time of the development of eruptions in this case was atypical. Suggested mechanism of skin toxicity in targeted therapies was direct toxic effect, and blockage of the target receptors on the surface of cells.[8] In our case, epidermal and dermal layers appear to be affected similar to HFSR. However, pathological findings of our case is not specific and can also be seen in broad spectrum of dermatological

diseases. Consultant of dermatology suggested that with this atypical findings, most probable diagnosis could be FDR and only rechallenge will provide evidence. After multidisciplinary evaluation, we treated patient with systemic steroid and stop the axitinib treatment. The lesions resolved significantly. We planned for rechallenge after few weeks, but we lost the patient with sudden cardiac death.

To the best our knowledge, this type of skin eruption is first described in literature. Though, findings of our patients are interesting, this report has limitation that couldn't describe exact pathogenesis of this skin reaction. But, when we searched the literature, we also couldn't find detailed information about exact pathogenesis of specific skin eruptions induced by targeted treatment. Thus, we didn't make any analogy from the literature. However, we try to describe the patient, lesions, our management strategy and treatment results. In conclusion, it is important to describe class type side effects from targeted therapy to build optimal toxicity management algorithms.

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