CASE REPORT

Sorafenib induced acral pigmentation: A new entity

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ABSTRACT

Sorafenib is a multikinase inhibitor commonly used for the treatment of advanced renal cell and hepatocellular carcinoma. The commonly reported dermatological adverse effects of Sorafenib include hand-foot syndrome (HFS), alopecia, pruritus, facial and scalp erythema, splinter hemorrhages, keratoacanthomas, squamous cell carcinomas and eruptive melanocytic naevi. We report a case of asymptomatic hyperpigmentation of the palms and soles in a patient receiving Sorafenib therapy for advanced renal cell carcinoma, in the absence of features of classic HFS, which has not been previously reported in the literature.

Key words: Acral pigmentation, hand foot syndrome, Sorafenib

INTRODUCTION

Sorafenib is a multikinase inhibitor which has been Food and Drug Administration approved for the treatment of advanced renal cell carcinoma and hepatocellular carcinoma but is also being used in locally advanced or metastatic patients with radioactive iodine-refractory differentiated thyroid cancer and is currently also in trial for use in desmoids tumours. It acts by inhibiting the Ras/Raf/MEK pathway which is a signalling cascade that controls cell growth and survival, ultimately affecting cellular proliferation, apoptosis, differentiation, and transformation.[1] Various cutaneous adverse effects like hand-foot syndrome (HFS), alopecia, pruritus, facial and scalp erythema, splinter haemorrhages, keratoacanthomas, squamous cell carcinomas and eruptive melanocytic naevi have been reported with Sorafenib therapy.[1-3] Herein, we present a case of Sorafenib induced hyperpigmentation of the palms and soles in a patient of renal cell carcinoma. HFS is a commonly reported adverse effect of Sorafenib, but such a pattern of asymptomatic acral pigmentation in the absence of features of HFS with Sorafenib has not been previously reported in the literature.

CASE REPORT

A 57-year-old female with renal cell carcinoma and malignant pleural effusion underwent radical nephrectomy. Postnephrectomy, she was started on Sorafenib 400 mg twice daily in view of the advanced nature of the disease. Within 6 weeks of initiation of therapy, the patient presented with progressive hyperpigmented macules over the palms and soles. The lesions were progressive and asymptomatic without any preceding history of symptoms like erythema, oedema, swelling, numbness, tingling, discomfort, pain or blistering over the affected sites. There was no history of any other systemic complaint or any drug intake. On examination, there was diffuse blotchy, macular hyperpigmentation over the palms, while over the soles it was more apparent along the lateral margins and nonpressure areas with relative sparing of pressure areas [Figure 1]. Other body sites including the dorsa of hands and feet, mucosae and nails were normal. All the routine haematological and biochemical parameters were within normal range. Biopsy for histopathological assessment was refused by the patient. The patient was reassured and was advised to use emollients while Sorafenib therapy was continued owing to the nonfatal nature of the rash and the advanced nature of the disease. The pigmentation persisted without any further progression over the next 2 months of therapy but further follow-up could not be done as the patient was lost to follow-up. Causality assessment was carried out using the Naranjo's scale and the World Health Organization-Uppsala Monitoring centre criteria after which we came to a conclusion that Sorafenib was the "probable" (Naranjo's score 5) cause of this adverse drug reaction.[4,5]

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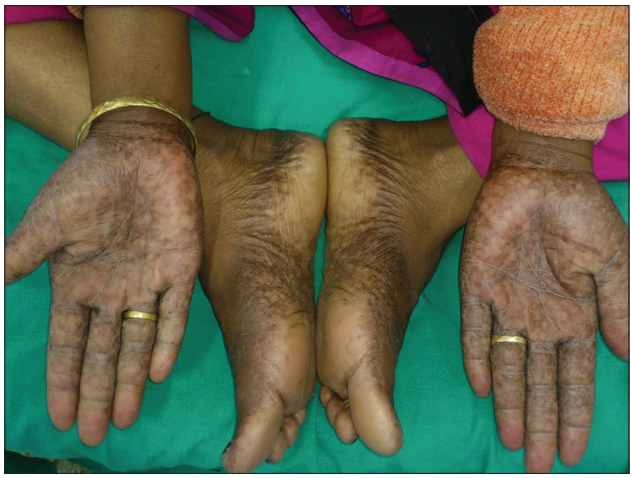

Figure 1: Sorafenib induced pigmentation over the palms and soles

DISCUSSION

Sorafenib belongs to a new class of anticancer drugs, namely multi-targeted oral small molecule tyrosine kinase inhibitors, which cause inhibition of tumor angiogenesis. It acts as a selective inhibitor of vascular endothelial growth factor receptor, platelet derived growth factor receptor-β, Raf and C-kit.[1,3] Apart from systemic adverse effects like abdominal symptoms, bleeding diathesis, anemia, weight loss, hypertension and neuropathy, a multitude of cutaneous adverse effects have also been reported with Sorafenib which include HFS, desquamation, alopecia, pruritus, xerosis, nail changes, loss of hair pigmentation, seborrhoeic dermatitis like rash, flushing, facial erythema, leucocytoclastic vasculitis, splinter haemorrhages, erythema multiforme, keratoacanthomas, squamous cell carcinoma and eruptive melanocytic naevi.[1-3]

Hyperpigmentation is a common adverse effect of various anticancer drugs with agents like busulphan, cyclophosphamide and hydroxyurea producing diffuse hyperpigmentation while tegafur and capecitabine have been reported to produce acral pigmentation.[6] The acral pigmentation described with anticancer drugs has been seen to appear characteristically over the pressure sites of palms and soles which has been attributed to the increased blood flow to these areas leading to an increased drug deposition.[7] The underlying pathogenesis of hyperpigmentation remains unknown but proposed mechanisms include: (a) Direct stimulation of melanocytes inducing melanin synthesis, (b) deficiency of tyrosinase inhibitors, (c) formation of stable drug-melanin complexes.[7] Sorafenib has been reported to induce pigmentary changes like skin lightening, loss of hair pigment and eruptive onset of melanocytic naevi but such a pattern of acral hyperpigmentation is unreported till date.[3,8]

Hand-foot syndrome is a commonly reported adverse effect of Sorafenib which has been classified into three grades. Grade I consists of minimal skin changes or erythema with swelling, dysesthesia or paresthesia without pain. Grade II is a progression of manifestations of Grade I, where pain and discomfort affect the daily activities of the patient. Grade III is the superimposition of blistering, moist desquamation, ulceration, and severe pain severely affecting the function.[8] Acral hyperpigmentation is not described as a classical presentation of HFS but there are various case reports of development of acral hyperpigmentation, isolated as well as progressing to frank HFS, with chemotherapy drugs like capecitabine in individuals with skin types IV-VI.[9,10] Many authors consider acral hyperpigmentation to be an early presentation of HFS especially in dark-skinned individuals, which may or may not progress to classical HFS.[10] As the characteristic erythema may be masked in dark skin individuals, few authors have even suggested that definition of Grade I HFS for black patients should be revised to include hyperpigmentation of the palms and soles instead of erythema.[9]

Our patient, a Fitzpatrick skin type V individual, presented with asymptomatic acral hyperpigmentation, 6 weeks after initiation of Sorafenib therapy. The pigmentation was progressive but rest of the skin, nails and mucosae remained uninvolved over the course of its progression. The pigmentation observed in our case was diffuse over the palms but characteristically spared the pressure areas over the soles. There was no preceding history of any inflammatory symptoms and on follow-up also there was no progression to classical HFS. The pathogenesis of acral hyperpigmentation in our case remains unclear and speculative. Owing to the absence of signs and symptoms of HFS and the sparing of pressure areas over the soles, it could be attributed to an isolated event unrelated to HFS. Another explanation could be that the pigmentation was an initial presentation of HFS which did not progress to the classical HFS.

CONCLUSION

Acral pigmentation is a rare, previously unreported adverse effect of Sorafenib which could either be an isolated finding unrelated to classical HFS or an atypical/initial manifestation of HFS.

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