Sorafenib-induced grade III hand–foot skin reaction with ulcerative dermatitis on scrotum, penis, and earlobe

Sir,

A 60-year-old male with grade III hepatocellular carcinoma taking sorafenib 400 mg twice daily since 10 days was referred to the dermatology outpatient department for erosions and ulcerations on scrotum, penis, and frictional zones like sacral areas and buttock. On dermatological examination, there were symmetrical erythematous patches with surface ulceration over groin, scrotum, penis, and gluteal region [Figure 1a and b]. In addition, erythematous plaques with central crusting and necrosis over bilateral earlobes were noted[Figure 1c and d]. On the background of decreased food intake due to hepatocellular carcinoma and clinical features, acquired zinc deficiency and sorafenib-induced hand–foot skin reaction were suspected. However, during hospital stay he developed new erythematous patches with characteristic perilesional halo over palmar aspect of all finger tips, toes, and heel [Figure 1e and f]. Few of these patches had central blistering and few were hyperkeratotic. All routine investigations were within normal limit except liver enzymes [total S. bilirubin 1.3 mg/dL, aspartate transaminase 194 U/L (0–37 U/L), alanine transaminase 80 U/L (0–40 U/L), alkaline phosphatase 800 U/L (100–290 U/L)]. His serum zinc level was 100 μg/dL (90–150 μg/dL). Histopathology from the erythematous patch revealed hyperkeratosis, focal parakeratosis, and irregular acanthosis with subcorneal bulla filled with neutrophils and fibrin. Papillary dermis showed mild lymphocytic infiltration [Figure 2]. Hence, final diagnosis of sorafenib-induced hand–foot skin reaction was made and the drug was discontinued. After 2 weeks, the skin lesions improved completely [Figure 3]. He was issued a drug card and capecitabine was started for hepatocellular carcinoma. On subsequent follow-up, the patient did not develop any similar skin lesions.

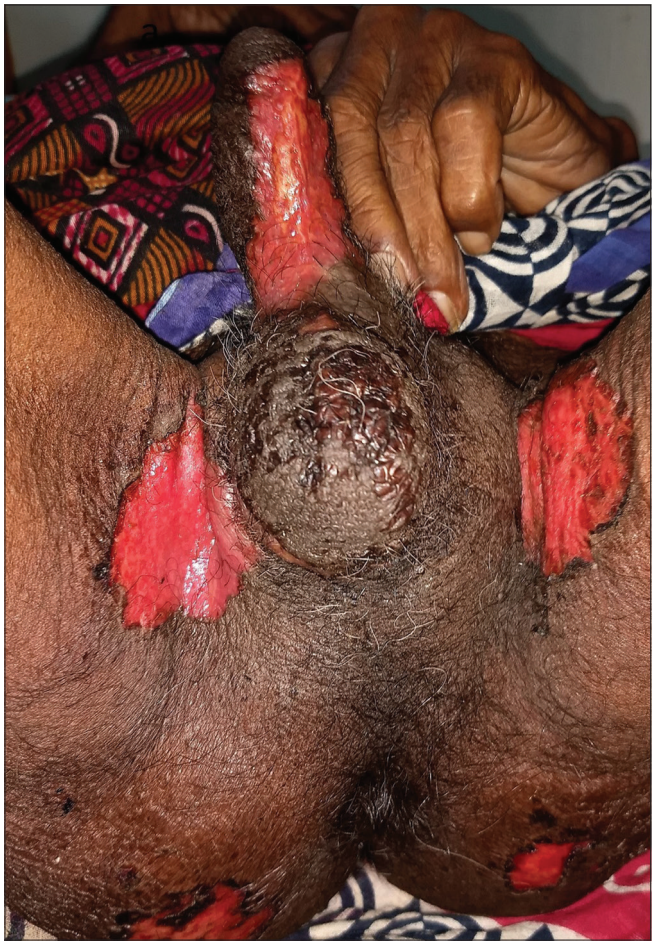

Figure 1a: Ulceration over groin, scrotum and under surface of penis

Sorafenib is a multikinase inhibitor, which has been recently approved for the treatment of carcinomas such as hepatocellular carcinoma.[1] Dermatological adverse events associated with sorafenib include hand–foot skin reaction, facial erythema (rash and desquamation), splinter subungual hemorrhage, alopecia, pruritus, and xerosis.[2] The prevalence of hand–foot skin reaction is 10%–62% in patients treated with sorafenib.[3] Clinically, hand–foot skin reaction develops within the first 2–6 weeks of treatment as hyperkeratotic lesions, with the formation of calluses and superficial blisters on an erythematous base, mainly affecting the palms and soles bilaterally. The lesions usually have a characteristic peripheral erythematous halo. Symptoms are dose-related and are noted in areas of skin subject to pressure or friction.[3]

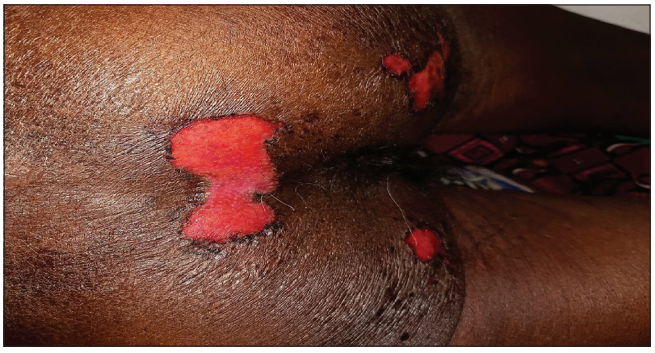

Figure 1b: Ulcerative dermatitis over gluteal area and frictional areas

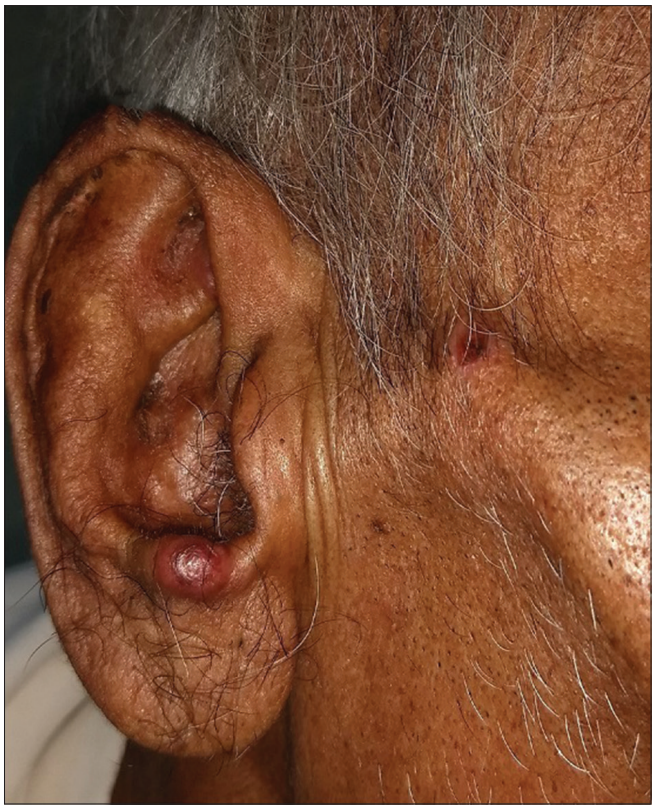

Figure 1c: Erythematous plaques with ulceration over right earlobe

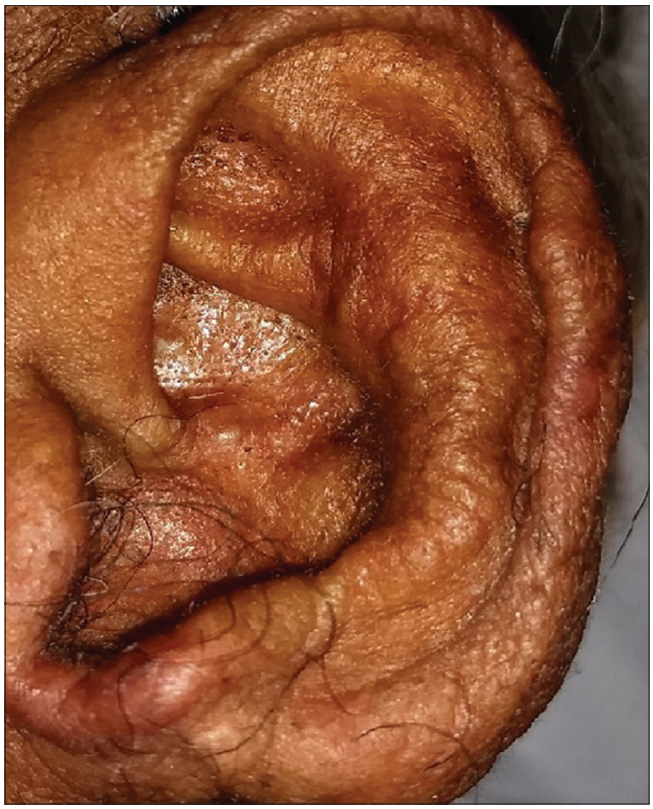

Figure 1d: Erythematous plaques with ulceration over left earlobe

We found only one previous case report of sorafenib-induced hand–foot skin reaction with scrotal lesion.[4] The National Cancer Institute has classified the lesions into three grades according to their severity. Minimal skin changes without pain (grade I), skin changes or pain, not interfering with function (grade II), and ulcerative dermatitis or skin changes with pain interfering with function (grade III). The majority of the cases are reported to be mild to moderate (grades I and II), responding to topical treatment with high-potency corticosteroids. Severe involvement, as in our patient, is less frequent and usually necessitates sorafenib discontinuation. The pathogenesis of acral erythema is still unknown, but the

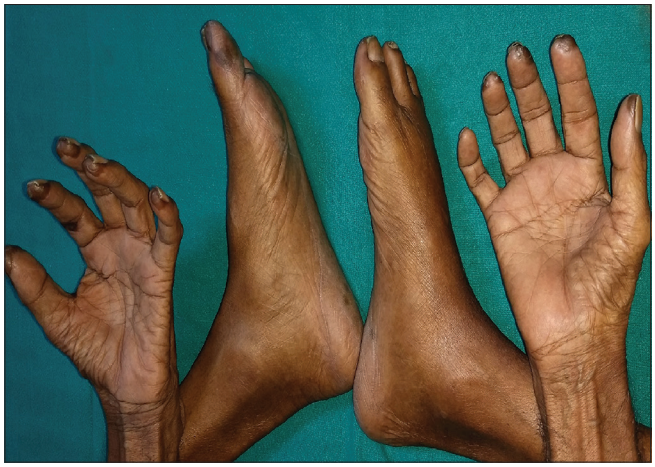

Figure 1e: Erythematous patches over all finger tips, toes and heel

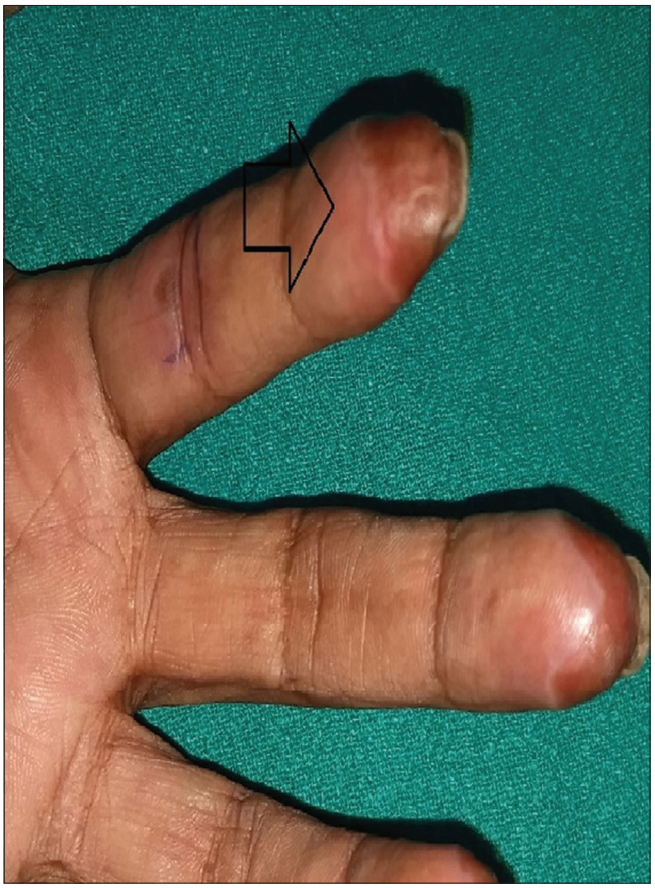

Figure 1f: Characteristic perilesional halo on finger tips

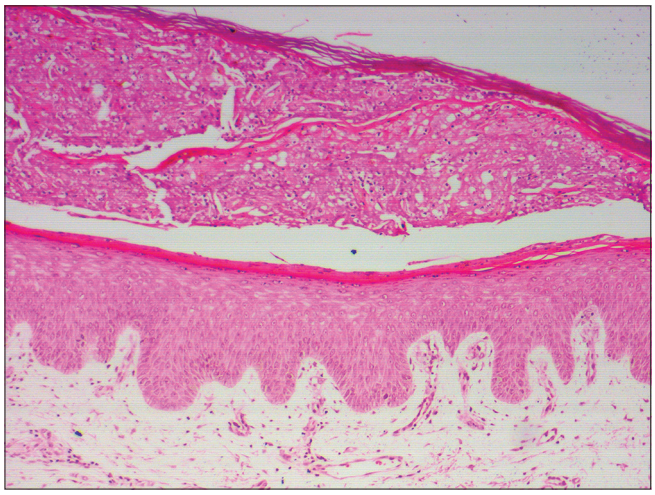

Figure 2: Hyperkeratosis, focal parakeratosis, irregular acanthosis with subcorneal bulla filled with neutrophils and fibrin (H and E, ×100)

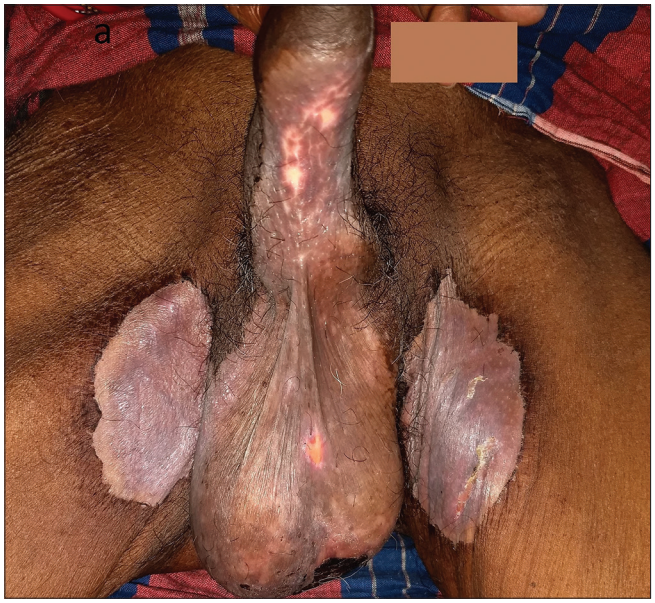

Figure 3a: Subsidence of ulceration after discontinuation of sorafenib

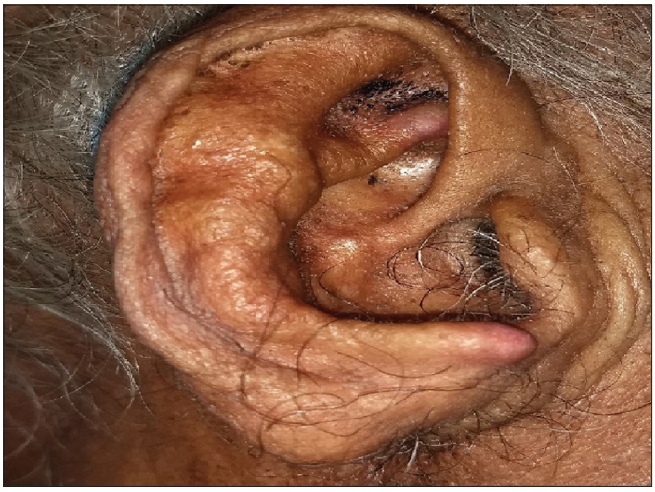

Figure 3c: Post treatment resolution of lesion on earlobe

dose dependence in most cases suggests a direct toxic effect. Another proposed mechanism is that subclinical trauma may result in leakage of the drug through capillaries and may inhibit vascular endothelial growth factor receptors and platelet-derived growth factor receptor–mediated capillary repair and regeneration, interfering with tissue regeneration. This hypothesis is supported by the appearance of lesions over sites of friction.[5] The diagnosis of this reaction is primarily based on temporal correlation of drug intake and clinical suspicion with lesions on the palms and soles. Histological examination is not necessary for diagnosis and shows epidermal parakeratosis and dyskeratosis with band-like areas of necrotic keratinocytes along with superficial bullous lesions. The treatment is mainly symptomatic for mild disease and a severe episode can require dose reduction, the temporary interruption of treatment, or even permanent withdrawal of the drug. In our case, the patient developed initially ulcerative dermatitis over frictional areas and earlobe instead of classical lesions of hand–foot skin reaction (erythematous patches with blistering and perilesional halo) over finger tips and sole. Although there is a single report of scrotal involvement associated with hand–foot skin reaction due to sorafenib, simultaneous presentation with ulcerative dermatitis over scrotum, penis, and earlobe has not been described previously in literature. Hence, the present case posed a diagnostic dilemma with acquired

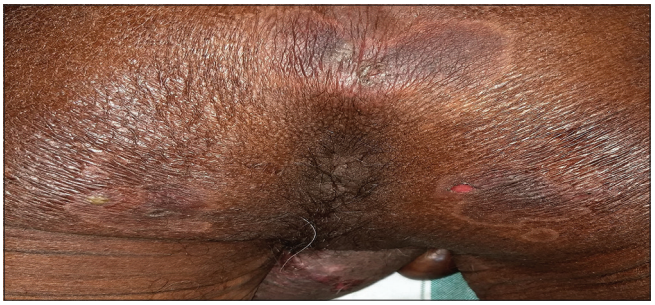

Figure 3b: Post treatment subsidence of ulceration

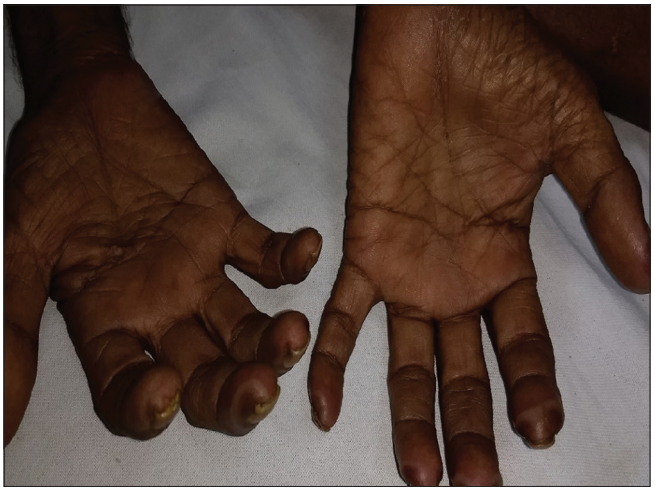

Figure 3d: Subsidence of erythema and perilesional halo

zinc deficiency at initial presentation until the appearance of classical lesions on finger tips. We believe the lesions on earlobes and scrotal skin is possibly due to induced trauma and capillary leakage of drug as proposed by Sibaud *et al*.[5] We report this case to emphasize the severe type of grade III hand–foot skin reaction due to a common chemotherapeutic drug (sorafenib) along with additional findings of ulcerative dermatitis over scrotum, penis, and earlobes.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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