Lower Limbs Erosions Induced by Sunitinib

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Sunitinib, a multi-targeted kinase inhibitor (MKI) affecting tumour cell angiogenesis and proliferation, has been approved for the treatment of gastrointestinal tumours and advanced renal cell cancer. However, approximately 80% of patients experience cutaneous side effects (1, 2). Leg erosions/ulcers have very occasionally been reported in patients treated with MKIs (3–6). We report a severe new case involving hand-and-foot skin reactions and subungual splinter haemorrhages that prompted us to withdraw sunitinib treatment.

CASE REPORT

A 55-year-old Caucasian man with advanced renal cell cancer with bone, lung and lymph node metastases was referred to us in November 2009 with acute painful ulceration of the lower limbs. His past medical history was notable for left nephrectomy (performed in 1989), renal cell cancer and type II diabetes. Sunitinib treatment (Sutent®, Pfizer, Paris, France) had been initiated 3 weeks prior to referral at a dose of 50 mg/day. One week later, he had developed painful fibrous and oozing erosive lesions with inflammatory borders on his legs (Fig. 1). Moreover, an examination revealed painful bilateral erythema of the palms and soles, bullous swelling of the soles (Fig. 2), keratotic paronychia and subungual splinter haemorrhages. Prior to this ulceration, there had been no underlying skin lesions including purpura, nor venous insufficiency or peripheral arterial disease. Superficial swabs were positive for methicillin-resistant *Staphylococcus aureus* and *Enterococcus* spp. The patient's oral, ocular and genital mucosae were free of lesions. The delay in onset

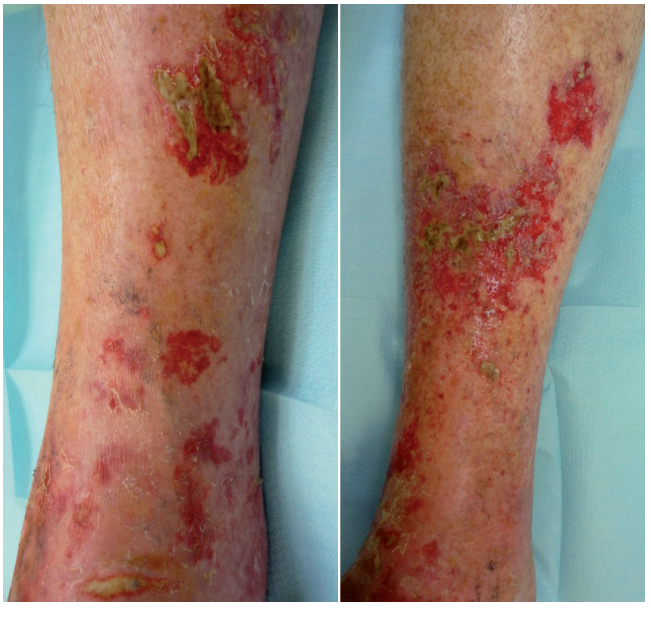

Fig. 1. Fibrous and oozing inflammatory erosions arising from sunitinib treatment.

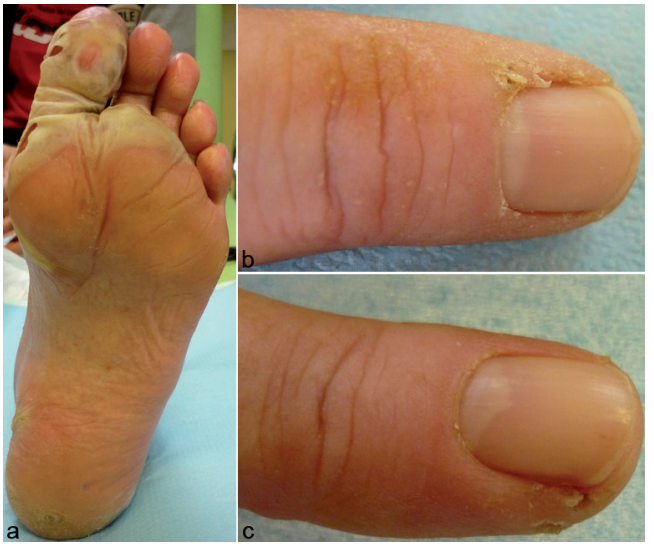

Fig. 2. (a) Erythema and bullous swelling of the sole. (b) Keratotic paronychia. (c) Splinter subungual haemorrhage.

and simultaneous occurrence of hand-and-foot skin reactions and subungual haemorrhages suggested cutaneous side effects related to sunitinib. No biopsy of the edge of the ulcers was performed. Ultrasound imaging ruled out venous insufficiency or peripheral arterial disease. Silver sulfadiazine and highly potent corticosteroid ointment were applied and sunitinib was withdrawn temporarily. Fifteen days later, the lesions had improved, but fibrous bilateral erosions remained, those on the three first metatarsophalangeal joints of the patient's left foot being especially severe. After a month and a half of disruption, sunitinib was reintroduced at a reduced dose (25 mg/day). Inflammatory erythema relapsed within 72 h around the remaining ulcers, prompting us to permanently withdraw sunitinib. Inflammation quickly regressed, but the erosions persisted. In January 2010, the patient developed, during the course of his disease, cutaneous leucocytoclastic vasculitis that was presumably related to the progression of his cancer. Systemic oral corticosteroid therapy (1 mg/kg/day) resolved the cutaneous purpura, but not the erosions. The patient died two months later.

DISCUSSION

Sunitinib is an oral MKI targeting VEGFRs 1–3, PDGFR-a, c-Kit, Flt-3, colony stimulation factor- receptor 1 and glial cell line-derived neurotrophic factor receptor (1, 2). It is responsible for cutaneous manifestations in 80% of patients (1). The two main complications, hand-and-foot skin reaction (36%) and stomatitis (36%), occur within the first month of treatment (1). Other manifestations include skin/hair discolouration (30%), facial swelling (24%) and subungual haemorrhages (10%), as well as various other complications

(facial acneiform eruption, lower leg oedema, alopecia, scalp dysaesthesia) (1). Signs in support of identifying sunitinib as the likely cause of observed leg erosions include: *i*) absence of prior history of lower limbs erosions, ulcers and classic causes of leg erosions; *ii*) delay of onset at least one week after sunitinib initiation; *iii*) simultaneous occurrence of other skin lesions that have previously been reported to be associated with sunitinib (hand-foot syndrome, splinter haemorrhages); *iv*) improvement after withdrawal of treatment; *v*) and recurrence after its reintroduction.

Three cases of necrotic ulceration of the lower limbs linked to sunitinib, and one associated with a second MKI, sorafenib, have previously been reported between 8 days to 42 days after the initiation of treatment. Durant et al. (3) described the case of a 50-year-old woman with sensory neuropathy who developed necrotic ulcers in the extremities (hands and feet) one month after the initiation of sunitinib therapy. Separately, Feyerabend et al. (4) reported a necrotic infection of the foot 8 days after the initiation of sunitinib treatment in a patient with type II diabetes that ultimately necessitated amputation. Guyot-Caquelin et al. (5), meanwhile, reported a 73-year-old woman with a history of deep venous thrombosis of the right leg who developed chronic ulcers in the same leg 6 weeks after starting sunitinib. Richetta et al. (6) reported a case of painful ulcers on elbow and lower limb 20 days after the initiation of sorafenib treatment. We confirm the lack of a clear dose relationship as our patient relapsed at a half-dose. In two previous cases (3, 4), skin necrosis of the extremities could be considered a severe variant of hand-and-foot skin reaction. The present case bears similar features, with our patient simultaneously developing hand-and-foot skin reaction and skin ulcers. However, as in other cases (5, 6), he presented lower limb erosions at a distance from the extremities, raising doubts as to whether or not they are a distinct complication from hand-and-foot skin reaction.

The pathogenetic basis of these complications is far from being clear. Erosions/ulcers may be the consequence of skin ischaemia related to a decrease in cutaneous blood microcirculation. A biopsy performed by Guyot-Caquelin et al. (5) revealed the presence of a massive neutrophilic infiltration of the dermis without vasculitis or thrombosis. Neoangiogenesis is crucial in the healing of the skin. Its impairment is responsible for impaired wound healing of repeated daily traumas to the lower limbs (5). Moreover, it has been suggested that underlying microangiopathy and neuropathy may act as precipitating factor for erosions/ulcers (3). This hypothesis is supported by our case and others (4, 6). These cases all involved patients with type II diabetes, leading us to speculate that pre-existing diabetic microangiopathy may have played a role in the observed reactions. Lastly, sunitinib may also interfere with contractile interactions between fibroblasts and the surrounding extracellular matrix, by modifying the differentiation of fibroblasts into contractile myofibroblasts and their synthesis of contractile proteins (7). It is not possible to draw any conclusions as to the possible relationship between the occurrence of lower limb ulceration and efficacy against tumours as sunitinib is usually withdrawn when symptoms occur.

Sunitinib should be added to the list of anti-neoplastic drugs that can induce cutaneous erosions/ulcers, which already includes methotrexate (8). Complications can be severe and may lead to the permanent withdrawal of treatment. Physicians should be aware of the potential for severe cutaneous complications in patients with pre-existing neuropathy or microangiopathy.

The authors declare no conflict of interest.

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