

Scrotal Cutaneous Side Effects of Sunitinib

TO THE EDITOR: Sunitinib is an oral, multitargeted kinase that blocks the receptors for vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and stem-cell factor (c-kit). Sunitinib was approved in 2006 for the treatment of advanced renal-cell carcinoma and gastrointestinal stromal tumors. In clinical trials, dermatologic adverse effects included the acral syndrome (the hand-foot syndrome), seborrheic dermatitis-like eruption, rash, skin discoloration, and hair-color changes, with a prevalence of less than 15%.¹ From October 2005 to June 2007, a total of 40 patients with renal-cell carcinoma, included in a prospective clinical trial and expanded-access program with sunitinib (50 mg daily for 4 weeks at a time, alternated with 2-week intervals of no drug administration), were followed for dermatologic adverse events as defined by the National Cancer

Institute Common Toxicity Criteria (version 3.0). Dermatologic toxic effects (grade 2 or 3) with clinical or therapeutic consequences were investigated by means of photographs and skin biopsy.

We report on 5 of the 40 patients (12.5%), who had dermatologic toxic effects in both the scrotal and inguinal areas. Erythema and desquamation (Fig. 1A and 1C) appeared at a median of 66 days (range, 17 to 115) after exposure. The first clinical signs appeared 2 weeks after the initiation of sunitinib treatment, with a maximal intensity at week 4. The process was reversible, with a decrease in severity or disappearance of the lesions after a 2-week period during which the drug was not used (Fig. 1D). The dermatologic toxic effects reappeared with a similar delay in onset after reintroduction of the drug. Three patients without a history of psoriasis had severe scrotal

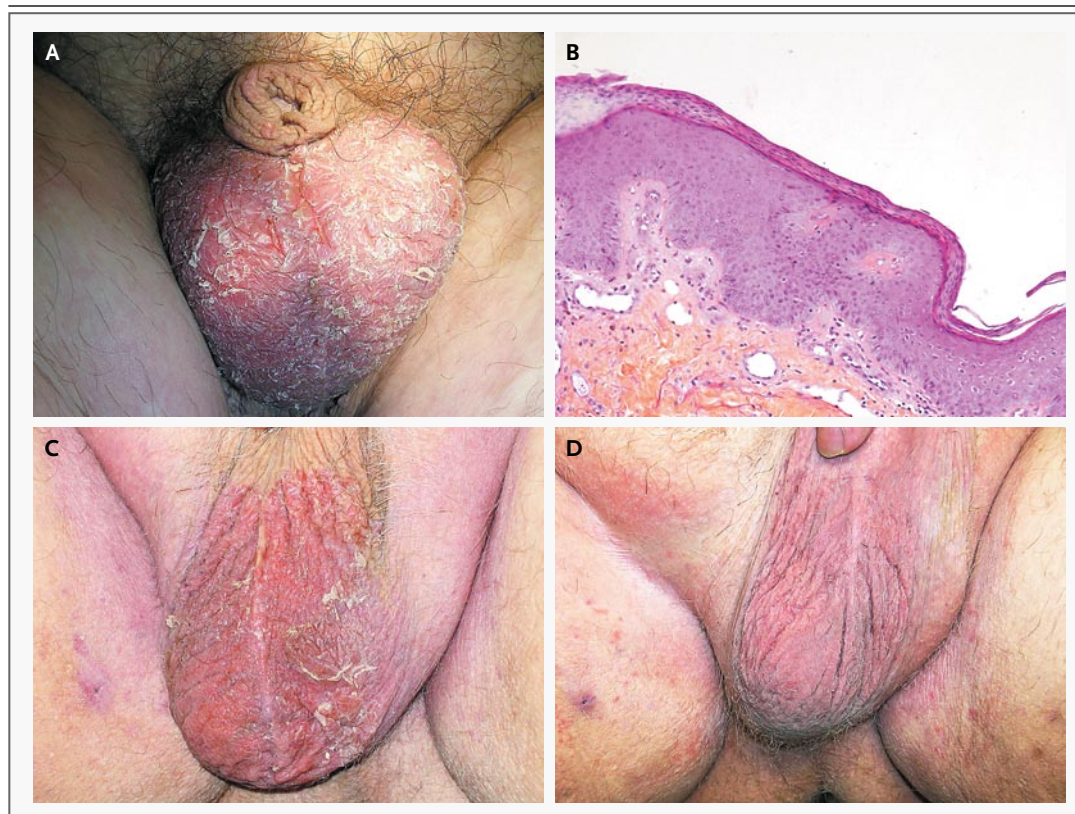


Figure 1. Symptoms and Resolution of Symptoms after Temporary Withdrawal of Sunitinib.

One patient had scrotal desquamation and erythema associated with bleeding (Panel A). A skin-biopsy specimen showed acanthosis and parakeratosis (Panel B, hematein-eosin stain). In another patient, skin lesions after 4 weeks of sunitinib treatment (Panel C) partially resolved after a 2-week rest period (Panel D).

skin manifestations with pain, necessitating a decrease in the sunitinib dose to 37.5 mg. Histologic analysis of three biopsy specimens of scrotal lesions revealed acanthosis and parakeratosis without necrotic keratinocytes, findings that mimic the pathological features of psoriasis (Fig. 1B). Analysis of swabs of the scrotal folds and skin ruled out candidiasis.

Skin lesions localized to this area, which is richly supplied with vasculature and prone to both friction and trauma, could be linked to VEGF inhibition. The mechanisms are unknown, but some hypotheses suggest a key role of VEGF and hypoxia-inducible factor 1 α (HIF-1 α).² In patients with psoriasis, HIF-1 α is strongly up-regulated, and angiogenesis induced by VEGF plays an important role.³ Increased plasma levels of VEGF were reported in vivo after sunitinib treatment in patients with renal-cell carcinoma.⁴ As a consequence of the diffusion limit of oxygen within tissues, the antiangiogenic process could be associated with a paradoxical increase in hypoxia in both normal and tumor tissues.

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The above letter was referred to Pfizer, the manufacturer of sunitinib, which offers the following reply:

TO THE EDITOR: Billemont et al. describe a single-institution review in which 5 of 40 patients had

dermatologic changes while receiving sunitinib for renal-cell carcinoma. Dermatologic effects of sunitinib have been reported previously and are described in the package insert; these changes include skin discoloration, rash, the hand-foot syndrome, dry skin, and hair-color changes.¹ A previous report of a patient with renal-cell carcinoma and psoriasis showed “remarkable improvement in psoriatic plaques while on treatment with sunitinib.”² That report generated a hypothesis that antiangiogenic therapy in patients with psoriasis would be of benefit, whereas the findings in the five patients described here suggest the opposite hypothesis: that is, that antiangiogenic therapy may induce psoriasis-like lesions. Although differences such as the topographic characteristics of the lesions might explain these contradictory hypotheses, more research is needed to understand the possible relationship between an agent such as sunitinib and such lesions.

In order to begin early management of skin effects of sunitinib, physicians should be alert that some patients may hesitate to mention genital or perineal symptoms. Balancing individual safety and efficacy is critical for patients with diseases such as advanced renal-cell carcinoma. The benefit-risk profile of sunitinib in advanced renal-cell carcinoma has been established through large, randomized clinical trials evaluating the drug's safety and efficacy. In a phase 3 study of 750 previously untreated patients with advanced renal-cell carcinoma who were randomly assigned to receive either sunitinib or interferon, sunitinib was associated with improvement in the primary end point of progression-free survival (median progression-free survival, 11 months, vs. 5 months in the interferon group; hazard ratio for disease progression with sunitinib vs. interferon, 0.42; $P < 0.001$).³

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