Severe Photosensitivity Causing Multifocal Squamous Cell Carcinomas Secondary to Prolonged Voriconazole Therapy

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A 32-year-old woman was treated with long-term voriconazole therapy for recurrent aspergillosis associated with chronic granulomatous disease. A short time after commencement of voriconazole therapy, a severe photosensitivity reaction developed. Continued voriconazole exposure led to the development of multifocal facial squamous cell carcinomas. The photosensitivity reaction resolved after the patient changed therapy to posaconazole.

Case report. The patient, a 32-year-old white woman, received a diagnosis of chronic granulomatous disease and hyper IgE syndrome when she was 6 years old. She presented with pyoderma grangrenosum and left ulnar and right femoral osteomyelitis caused by *Aspergillus fumigatus* [1]. When the patient was 19 years old, she developed recurrent multifocal cerebral, spinal epidural, and paravertebral abscesses associated with extensive vertebral osteomyelitis caused by *A. fumigatus*, despite aggressive therapy with amphotericin B (both desoxycholate and liposomal formulations), surgery, and long-term maintenance therapy with itraconazole (up to 1800 mg/day) and IFN-γ (2 × 10⁶ U 3 times per week). When the patient was 29 years old, voriconazole therapy was obtained for compassionate reasons, and therapy commenced at 400 mg every 12 h. Immediately following the introduction of voriconazole therapy, an erythematous photosensitivity reaction affecting all sun-exposed skin developed. No other medications could be implicated, and voriconazole therapy, given the absence of alternative maintenance antifungal agents, was continued. Emollient, anti-inflammatory, and high-level sun protection creams were administered and advice to avoid sun exposure was provided. The severe photosensitivity reaction progressed, and 3 years later, the patient developed a squamous cell carcinoma (SCC) on her upper lip. During this time, there were no further relapses of infection. Two requests for compassionate access to posaconazole therapy were refused by the manufacturer during a period of 18 months. Within 12 months, multifocal, highly invasive SCCs developed on her nose and cheek (figure 1) that required radical destructive surgery, involving the removal of the nasal bones and septum, the formation of mucosal and skin flaps, and radiotherapy. After the surgery, a third request for compassionate access to posaconazole therapy was approved. Within 14 days of the commencement of therapy, the photosensitivity reaction completely resolved, and it has not recurred after 10 months of posaconazole therapy.

Discussion. Voriconazole, a broad-spectrum azole antifungal agent, has been associated with dermatological complications, mostly mild skin rashes. Severe reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis, have been occasionally reported [2–4]. Photosensitivity reactions, such as erythema, cheilitis, hyperpigmentation of the hands, exfoliative dermatitis, discoid erythematous lesions, pseudo-

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Figure 1. Extensive facial squamous cell carcinomas in a patient with voriconazole-induced photosensitivity reaction.
porphyria, and discoid lupus vulgaris, have also been infrequently reported [5–10, 13–15]. Although solar elastic changes, multiple lentigines, and ephelides in sun-exposed areas have complicated photosensitivity reactions from prolonged voriconazole exposure [10, 11], no cases of multifocal and highly invasive SCCs complicating voriconazole-induced photosensitivity reactions have been documented.

Of the other *Aspergillus*-active azole agents, only itraconazole has also been associated with a photosensitivity dermatitis [16] but not with the development of skin malignancies. The mechanism of voriconazole-induced photosensitivity remains uncertain, but the photosensitivity reactions may be a direct effect of voriconazole therapy or one of its metabolites or, alternatively, an indirect retinoid effect of voriconazole therapy [5,6,10,11]. Such photosensitivity reactions appear to be idiosyncratic, rather than dependent on dose [3]. Long-term voriconazole therapy has not previously been reported to be associated with skin malignancy [17, 18]. For our patient, the long-term voriconazole exposure and, consequentially, the prolonged photosensitivity reaction in the context of high, year-round ultraviolet exposure were likely important predispositions to the development of the SCCs. Although the underlying chronic granulomatous disease may have, in part, predisposed the patient to the photosensitivity reaction [11–14], no association with SCCs has been reported.

In summary, we highlight that, when complicated by a photosensitivity reaction, prolonged voriconazole therapy, particularly in the context of significant ultraviolet exposure, causes risk of the development of multifocal invasive SCCs. Therefore, in such contexts, an alternate agent should be used whenever possible.

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