Melanoma Associated With Long-term Voriconazole Therapy

A New Manifestation of Chronic Photosensitivity

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Background: Voriconazole is a triazole antifungal agent approved by the US Food and Drug Administration for serious fungal infections, including with Aspergillus, Fusarium, Pseudallescheria, and Scedosporium species. In initial clinical trials, approximately 2% of patients developed cutaneous reactions, including photosensitivity, cheilitis, and xerosis. Subsequent reports have implicated voriconazole as a cause of severe photosensitivity and accelerated photoaging, pseudoporphyria cutanea tarda, and aggressive squamous cell carcinoma.

Observation: We report 5 melanoma in situ lesions in the setting of extreme photosensitivity associated with long-term voriconazole therapy.

Conclusions: We recommend surveillance for skin cancer formation in all patients who require long-term voriconazole treatment, particularly those who manifest signs or symptoms of photosensitivity or chronic photodamage. Further study of the mechanism underlying voriconazole photosensitivity and oncogenesis is warranted.

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Voriconazole is a second-generation triazole antifungal agent that acts through inhibition of cytochrome P450–dependent ergosterol synthesis, a key step in fungal cell membrane lipid formation. Voriconazole was approved by the US Food and Drug Administration (FDA) in 2002 for the treatment of serious fungal infections, including with Fusarium and Aspergillus species. It also has demonstrated efficacy in esophageal candidiasis and in endemic mycoses such as histoplasmosis and coccidioidomycosis. In clinical trials for invasive aspergillosis, voriconazole demonstrated superior cure rates to amphotericin B and decreased toxic effects. Voriconazole therapy is generally well tolerated; the most common adverse effects include visual disturbances, gastrointestinal complaints (nausea, vomiting, and diarrhea), and cutaneous eruptions. Although photosensitivity was initially described in 1% to 2% of patients on long-term voriconazole regimens (>12 weeks of consecutive therapy), numerous reports in the literature have described pseudoporphyria, photoaging with multiple lentigines, and premature dermatoheliosis. Furthermore, several recent reports of aggressive squamous cell carcinoma (SCC) have been described following voriconazole administration. Herein, we describe 5 melanoma in situ lesions arising in areas of chronic photodamage in 2 patients receiving long-term voriconazole therapy.

Case 1

A 39-year-old woman with Fitzpatrick type III skin was referred to the University of California, San Francisco (UCSF), Department of Dermatology in May 2007 for severe photosensitivity and extensive lentigines on the photoexposed surfaces of the face, upper trunk, and extensor extremities. Prior to the development of photosensitivity, the patient worked in the field as a California Highway Patrol officer. She reported that she enjoyed spending time in the sun and had used tanning beds episodically between ages 23 and 30 years but was not actively seeking sun exposure or using tanning beds at the time of presentation to our clinic. She denied a history of frequent sun exposure as an adolescent or teenager and reported...
that she only sunburned on very rare occasions (less than once per year). She had no history of photosensitivity, melanoma, or nonmelanoma skin cancer prior to voriconazole therapy. There was no family history of skin cancer or photosensitive conditions.

In August of 1992, she was diagnosed as having coccidioidomycosis meningitis while residing in the Central Valley region of California. She was otherwise healthy, was not known to be immunodeficient, and resided in an area endemic for coccidioidomycosis. She had been maintained on oral fluconazole therapy until February 2004, at which time her infection became resistant to this therapy, and she required hospitalization. The fluconazole was replaced with oral voriconazole, 300 mg, twice daily, which she continued taking for the 3 years until her dermatologic evaluation. She initially was seen by an outside dermatologist in August of 2004 with a photodistributed vesicular eruption for which clinical presentation and histopathologic findings were consistent with pseudoporphyria, which was attributed to voriconazole.

Approximately 1 year after the voriconazole treatment was started, and continuing for the following 2 years, severe erythema developed in sun-exposed areas, and eruptive new pigmented macules appeared on the face, upper trunk, and extensor extremities. In January of 2007, after 35 months of voriconazole therapy, biopsy specimens taken from a 5-mm erythematous and brown macule on the right helix revealed a compound melanocytic neoplasm with evidence of regression; histopathologic findings from a subsequent reexcision demonstrated residual melanoma in situ (Figure 1). A 6-mm tan and erythematous macule on the dorsal surface of the patient’s left wrist was also biopsied at this time, and the specimen was interpreted to indicate an atypical lentiginous compound melanocytic nevus. Because this lesion extended to the periphery of the biopsy area, it was reexcised, but no residuum was identified.

At the time of presentation to the UCSF clinic, the patient had been taking hydroxychloroquine, 200 mg, by mouth twice daily for 25 months, as prescribed by her referring dermatologist, and applied mexoryl-based sunscreen daily (Anthelios; LaRoche-Posay, New York, New York), both for the management of her chronic photosensitivity. However, she acknowledged poor compliance with sun avoidance. She described ongoing severe erythema in sun-exposed areas as well as the progressive appearance of brown macules on her face, chest, and arms. Her medications on presentation included voriconazole, hydroxychloroquine, valacyclovir, levonorgestrel-ethinyl estradiol, and hydrochlorothiazide. Hydrochlorothiazide had been prescribed approximately 4 years prior for idiopathic lower extremity edema. Because of the potential for hydrochlorothiazide to cause photosensitivity, it was subsequently replaced by spironolactone and torsemide. However, her photosensitivity was unchanged following discontinuation of hydrochlorothiazide treatment.

Physical examination at the time of her initial visit revealed diffuse erythema and hyperpigmentation of the face, trunk, and extremities with a photodistributed accentuation. Innumerable tan pigmented macules were seen on the face, anterior chest, upper back, and extremities (Figure 2). Two hyperpigmented macules overlying the right mandible and the left forearm, each with an irregular border and greater pigmentation than the patient’s background lesions, were clinically suggestive of melanoma. Histopathologic analysis identified a solar lentigo with superimposed postinflammatory pigmentary alteration on the mandible and a lentiginous junctional melanocytic nevus with many associated superficial dermal melanophages on the arm.

Figure 1. Melanoma in situ, right ear (case 1). Single atypical intraepidermal melanocytes are seen in an irregular pattern along the dermoepidermal junction (hematoxylin-eosin, original magnification ×100).

Figure 2. Phototoxic effects and accelerated photoaging associated with chronic voriconazole therapy. Erythema, dermatoheliosis, and lentigines of the central chest (A), forearm (B), and dorsal surfaces of the hands (C) in a 39-year-old woman (case 1).
Five months later, the patient was seen at our pigmented lesion clinic with an ill-defined, 3.7 × 3.3-cm brownish-blue patch within a field of solar lentigines on severely sun-damaged skin on the mid-upper chest. A biopsy specimen demonstrated melanoma in situ, clinically consistent with lentigo maligna type. The patient underwent Mohs surgery with successful clearance. Permanent section from a debulking specimen demonstrated melanoma in situ without any evidence of an invasive component. The patient was diagnosed in September 2009 with 2 additional in situ melanomas, one on the right forearm and the other on the dorsal surface of the left hand, and underwent Mohs micrographic surgery for both lesions.

Following the second melanoma in situ diagnosis, voriconazole treatment was discontinued and therapy with fluconazole restarted. When fluconazole treatment led to alopecia, it was discontinued in October 2009, and treatment with itraconazole (200 mg, 3 times daily) was initiated. The patient plans to undergo close surveillance for additional melanomas that includes a total skin examination every 3 to 6 months in our clinic.

CASE 2

A 21-year-old man with Fitzpatrick type III skin and chronic granulomatous disease (CGD) began treatment with voriconazole, 200 mg, by mouth twice daily in March 2003 for pulmonary Aspergillus infection. The patient denied photosensitivity or a history of sunburn prior to voriconazole therapy. However, approximately 2 years after starting voriconazole treatment, he began to develop lentigines on sun-exposed areas of the body, including his face, forearms, and dorsal surfaces of his hands. He recalled an episode of blistering of both his upper and lower lips after a vacation in Florida in 2005. The patient reported that after starting voriconazole treatment, the sun seemed to bother him, and he subsequently avoided extensive sun exposure.

He did not have a family history of sun sensitivity, extensive lentigines, or melanoma, but his older sister was diagnosed as having basal cell cancer at age 19 years. He had been taking trimethoprim/sulfamethoxazole since age 5 days for bacterial prophylaxis following the diagnosis of CGD (dose at the time of presentation, 80 mg/400 mg, twice daily), but he denied photosensitivity while on this treatment regimen prior to beginning voriconazole treatment. The patient also was treated with oral isotretinoin, 30 mg/d, for approximately 6 months in 2007.

After approximately 55 months of voriconazole treatment, when the patient was 20 years old, an irregular, darkly pigmented macule was noted on his left forearm. A skin biopsy specimen revealed melanoma in situ; subsequent reexcision was performed 1 month later. Histopathologic analysis revealed cytologically atypical melanocytes arranged in nests and singly along the dermoepidermal junction, with pagetoid spread highlighted by a MART-1 stain (melanoma antigen recognized by T cells) (Figure 3).

On physical examination, he was found to have extensive brown, evenly pigmented lentigines varying in size between 2 and 10 mm. They involved photoexposed areas, including the face and dorsal surfaces of the hands and forearms (Figure 4). He had a well-healed scar on his left arm at the site of a previous melanoma in situ excision without residual pigmentation. Several months after his melanoma diagnosis, his antifungal therapy was changed from voriconazole to posaconazole. No subsequent lesions suggestive of malignancy were identified. The patient also described fading of the lentiginous pigmentation since he discontinued voriconazole therapy.

COMMENT

Following approval of voriconazole by the FDA in 2002, several case reports documented severe photosensitivity similar to that described by our patients. A constellation of findings is characteristic of photosensitivity to voriconazole, including development of lentigines, photosensitivity, and an increased risk of melanoma in situ, which requires close surveillance for future lesions.
Exposure in the presence of an inciting chromophore. The sunburn-like erythema and tissue edema following sun exposure is not known. The reaction pattern most closely resembles photosensitivity. 4 patients were not using any concurrent photosensitizing agents. Three patients were also taking trimethoprim/sulfamethoxazole, including actinic keratosis and lentigo formation. Each patient also developed SCC of the nose and cheeks the following year. The patient was not reported to be using any other photosensitizing agents. Despite sun avoidance and sunscreen use, she developed SCC of the upper lip after 3 years of voriconazole therapy.

In the third case, a 29-year-old woman with CGD was treated with voriconazole for disseminated Aspergillus infection, and she subsequently developed erythema on areas of UV exposure. The patient was not reported to be using any other photosensitizing agents. Despite sun avoidance and sunscreen use, she developed SCC of the upper lip after 3 years of voriconazole therapy as well as multiple additional SCCs of the nose and cheeks the following year.

Although each of the 3 patients had some form of immune compromise that may have predisposed the individuals to cutaneous malignancy (CGD, HIV/AIDS, and iatrogenic immunosuppression post-retransplant, respectively), in each case prominent photosensitivity and a temporal correlation between onset of therapy and the appearance of malignancy strongly implicated a contributing role of voriconazole.

In the fourth case report, our research group recently described 8 immunocompromised patients, including 2 children, who developed 51 cutaneous SCCs while receiving long-term voriconazole therapy. In several patients, aggressive high-risk tumors developed. Each patient also manifested additional signs of accelerated photodamage, including actinic keratosis and lentigo formation. Three patients were also taking trimethoprim/sulfamethoxazole, and 1 was taking dapsone; however, 4 patients were not using any concurrent photosensitizing agents.

The mechanism of voriconazole-induced photosensitivity is not known. The reaction pattern most closely resembles photos toxic effects, which typically manifest as sunburn-like erythema and tissue edema following sun exposure in the presence of an inciting chromophore. The
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REFERENCES