Phototoxicity, Pseudoporphyria, and Photo-onycholysis Due to Voriconazole in a Pediatric Patient With Leukemia and Invasive Aspergillosis

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Voriconazole is a triazole antifungal agent superior to amphotericin B in the treatment of invasive aspergillosis. It is generally well tolerated and has excellent oral bioavailability, providing significant benefit in the treatment of invasive fungal infections. There have been numerous reports of dermatologic reactions to this agent, including erythroderma, cheilitis, Stevens-Johnson syndrome, discoid lupus erythematosus, pseudoporphyria, squamous cell carcinoma, and photosensitivity reactions.

Pseudoporphyria, a dermatologic condition mimicking porphyria cutanea tarda, has been described as an adverse effect of voriconazole use [1, 2]. Clinical findings include photosensitivity, vesicles, bullae, milia, and scarring in sun-exposed areas [2]. Photo-onycholysis is a phenomenon of nail discoloration and onycholysis that has been described in the setting of a phototoxic drug reaction and pseudoporphyria [3]. Implicated drugs have most commonly been tetracyclines, fluoroquinolones, and psoralens; others have been reported as well [4].

We report a case of a pediatric patient with leukemia who developed symptoms consistent with pseudoporphyria and later photo-onycholysis while being treated with voriconazole. To our knowledge, this is the first reported case of pseudoporphyria due to voriconazole in a pediatric patient and the first reported case of photo-onycholysis as a consequence of voriconazole use.

Key words. photo-onycholysis; phototoxicity; pseudoporphyria; voriconazole.

CASE REPORT

Our patient is a previously healthy 9-year-old boy who was diagnosed with standard-risk pre-B acute lymphoblastic leukemia in April 2012. Induction was complicated by primary cutaneous aspergillosis requiring operative debridement and therapy with voriconazole. Angioinvasion of the dermal vasculature was evident on surgical pathology specimens. Four surgical procedures over a 10-day span were required to control the infection, the last using frozen sections to ensure negative margins. Voriconazole was continued through September of 2012, when he developed ventricular ectopy with short runs of ventricular tachycardia attributed to hypokalemia and hypomagnesemia. Because voriconazole and posaconazole are associated with ventricular bigeminy and prolongation of the QT interval, azole therapy was discontinued in favor of prophylaxis with daily intravenous micafungin. He subsequently developed repeated catheter-related blood-stream infections (CR-BSIs) requiring inpatient admission and replacement of his implanted port. In May of 2013, micafungin was discontinued and oral voriconazole was resumed to reduce the risk of CR-BSIs. The dosage required several adjustments due to alternately inadequate and supratherapeutic trough levels.

He was admitted to the Oncology service in June 2013 with a bullous lesion (Figure 1A) with a small area of surrounding erythema on his right lateral malleolus as well as fever and reluctance to bear weight. Magnetic resonance imaging of the ankle and foot did not demonstrate any
evidence of joint effusion, soft tissue abscess, or osteomyelitis. Also noted at that time was peeling skin affecting his face; the desquamated areas were pink. A clinical diagnosis of cellulitis was made. He improved rapidly on parenteral vancomycin and cefepime and completed treatment with a 14-day total course of clindamycin and levofloxacin.

A biopsy of the cutaneous eruption exhibited keratinocyte maturational disarray, rare dyskeratotic cells, and occasional mitotic figures, features consistent with a phototoxic eruption (Figure 1B and C). These results suggested that the bullous lesion secondary to phototoxicity provided a portal of entry for bacterial superinfection. The decision was made to continue oral voriconazole to avoid the risk of recurrent CR-BSI with intravenous antifungal therapy. His voriconazole trough drawn early in this hospitalization was 0.2 µg/mL, prompting a dose increase. A subsequent trough was 0.3 µg/mL, prompting an additional dose increase.

One month later, he presented to Oncology clinic with new onset of rash and nail changes. There was extensive peeling of his arms, chest, and back where not covered by his shirt, on his anterior legs, and on the dorsal surfaces of his hands. Cheilitis was noted as well, with hemorrhagic crusting and desquamation of his lower lip. All fingernails of both hands demonstrated a distal crescent of onycholysis with brown hyperpigmentation without pain (Figure 2). The toenails were not involved. His family reported that, for the past several weeks, he had had only brief sun exposure, for example, while walking from the house to the car. Because it was summer, he generally wore short sleeves and shorts, but he wore only closed-toed shoes. The distribution of skin changes was limited to sun-exposed areas and was most intense on dorsal surfaces. The nail changes closely matched those described for photo-onycholysis [3].

Voriconazole was immediately discontinued. His serum level that day was supratherapeutic at 7.8 µg/mL. At follow-up 12 days later, the erythroderma and desquamation

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Figure 1. (A) Bullae on the right lateral malleolus with surrounding erythema. (B and C) Histologic features of the patient’s cutaneous biopsy. (B) Low-power view of the exhibiting epidermal acanthosis and hyperkeratosis with a scant perivascular inflammatory infiltrate. (C) High-power view showing keratinocyte dyskeratosis and maturational disarray consistent with a phototoxic eruption.

Figure 2. Polydactylous, distal crescent-shaped, photo-onycholysis Type I, with and without nail pigmentation affecting all fingernails. Both hands demonstrated a similar appearance. Evident in this photograph are desquamation, erythroderma, and hyperpigmentation of the dorsal skin surfaces.
had nearly resolved, and the nail changes were improving. He did not lose any of his nails. Because itraconazole has also been associated with photosensitivity, his antifungal coverage was changed to micafungin, which is being given during periods of anticipated neutropenia or high-dose steroid administration [5]. He has had no signs of relapse of aspergillosis, and his serum galactomannan has remained negative.

**DISCUSSION**

As an orally bioavailable, well tolerated agent, voriconazole has revolutionized the treatment of invasive fungal infections in immunocompromised hosts. Phototoxicity due to voriconazole is a well defined phenomenon, although photo-onycholysis has not previously been described as an adverse reaction to this agent. In a recent series of pediatric patients in Switzerland, phototoxicity occurred in 7 of 21 patients [6]. A dosing regimen exceeding 6 mg/kg per dose twice a day was associated with a significantly higher risk of phototoxicity. Nevertheless, dosing recommendations to achieve therapeutic troughs for children between 2 and 11 years of age is 9 mg/kg per dose, not to exceed 330 mg per single dose [7].

Photo-onycholysis can present as part of Segal’s triad of photosensitivity of the skin, discoloration of the nails, and onycholysis [3, 4, 8]. Drug-induced photo-onycholysis more commonly follows a skin photosensitivity reaction, but it has been described in the absence of skin manifestations [3]. Four distinct types of drug-induced photo-onycholysis have been described based on the distribution and appearance of the nails [3, 9]. No apparent relationship has been found between the offending drug and the different types of photo-onycholysis [3]. Clinical findings in our patient were consistent with Type I, with several fingers showing a half-moon-shaped and concave separation of the nail with well demarcated borders (Figure 2) [3, 9]. These characteristic nail changes develop due to acute toxicity to the nail bed epithelium. Pain preceding the nail changes is a common complaint, but it was absent in our patient. The pathogenic mechanisms are not clearly understood.

Voriconazole-induced pseudoporphyria has been successfully managed without discontinuing the agent [10]. In this scenario, an attempt was made to continue voriconazole after development of phototoxicity and bullous photodermatosis resembling pseudoporphyria. The patient developed progressive cutaneous manifestations, cheilitis, and onycholysis despite minimal sun exposure. Photo-onycholysis has been reported to regress spontaneously after discontinuing the offending agent, but in some cases it may persist after the drug has been withdrawn [9]. In our patient, symptoms improved almost immediately upon discontinuation of voriconazole.

Clinicians managing patients on long-term voriconazole must provide detailed education on avoidance of sun exposure and adequate skin protection, particularly during the warmer seasons. Given the risk of progression to a more serious reaction and the potential long-term risk of squamous cell carcinoma, serious consideration must be given to discontinuation of voriconazole as soon as a phototoxic reaction occurs [11].

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**References**