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Voriconazole-Induced Phototoxicity Masquerading as Chronic Graft-versus-Host Disease of the Skin in Allogeneic Hematopoietic Cell Transplant Recipients

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Abstract

Systemic fungal infections pose a significant risk to patients following allogeneic hematopoietic cell transplantation (alloHCT). Voriconazole (Vfend®, Pfizer) is an oral second-generation triazole antifungal agent that offers broad spectrum of coverage against fungal species and is frequently utilized in the post-HCT setting. Herein, we describe five patients who were initially believed to be experiencing a flare of cutaneous chronic graft-versus-host disease (cGvHD), but who were actually exhibiting phototoxicity caused by voriconazole. A high index of suspicion for this adverse reaction in the post-alloHCT setting will prevent misdiagnosis and avoid inappropriate therapy for cGvHD.

Introduction

Systemic fungal infections pose a significant risk to patients following allogeneic hematopoietic cell transplantation (alloHCT). In the early post-transplant period, neutropenia is the primary risk factor and frequently fluconazole is used as effective prophylaxis against Candida infections. Late after engraftment, however, the most important fungal infection is invasive aspergillosis, particularly during periods of active graft versus host disease and increased corticosteroid use [1,2]. Voriconazole (Vfend®, Pfizer), a second-generation oral triazole antifungal agent, is the treatment of choice for invasive aspergillosis [3], and its ease of administration and favorable safety profile have resulted in increased utilization as antifungal prophylaxis, especially when there is high risk for aspergillosis [4]. Like the other azole antifungals, voriconazole inhibits cytochrome P450-dependent 14-α-sterol demethylase, which is required for ergosterol biosynthesis, resulting in destruction of the fungal plasma membrane. It is effective against *aspergillus* sp, molds, and yeasts [5].

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Following FDA approval in 2001, expanded utilization of voriconazole has led to increased recognition of the drug's potential side effects, which include vision changes (20%), hallucinations (15%) hepatic enzyme abnormalities (12–20%), and skin reactions (17%) [5]. In preliminary clinical studies, a photosensitive rash was reported in only 2% of patients (41/2090) [5]. Herein, we describe five patients who were believed to be suffering from recalcitrant skin cGvHD, but who, were actually experiencing cutaneous phototoxicity caused by voriconazole. A high index of suspicion for this adverse reaction in post-alloHCT patients will facilitate the proper diagnosis and avoid inappropriate therapy for cGvHD.

Materials and Methods

In this retrospective analysis, five patients with cGvHD who developed voriconazole-associated phototoxicity were identified at the National Institutes of Health (NIH) dermatology service between May 2003 and August 2007. Medical records, clinical photography, and histological specimens were reviewed. Patient characteristics are summarized in Table 1.

Results

Patient 1 was a 15 year-old male diagnosed at age six with metastatic alveolar rhabdomyosarcoma. He underwent a matched nonmyeloablative allogeneic peripheral blood hematopoietic cell transplantation (alloPBHCT) following failure of multiple therapies. Acute cutaneous GvHD was confirmed by skin biopsy on day +8 post-transplant. Recurrent lichen planus-like cGvHD was noted at day +100, followed by vitiligo 20 months post-transplant **(**Figure 1A, B).

Thirty-two months post-transplant, voriconazole was initiated for a presumed pulmonary aspergillosis. Two months later, the patient developed bright erythema of the forehead, malar cheeks, hands, forearms, and arms, which his treating physicians attributed to a flare of skin cGvHD. At the time of his NIH evaluation, several erosions and intact bullae were also noted on the head, neck, arms, anterior legs, and dorsal aspects of both feet **(**Figure 1C, D).

A diagnosis of phototoxicity and drug-induced pseudoporphyria cutanea tarda (pseudo-PCT) secondary to voriconazole was made. Voriconazole was replaced by posaconazole and strict photoprotection was instituted. The bullae resolved in 3 weeks and the erythema gradually dissipated.

Patient 2 was a 6 year-old female who underwent a 5/6 mismatched unrelated myeloablative umbilical cord blood transplantation for pre-B cell acute lymphoblastic leukemia (ALL) 11 months before presenting to the NIH. Two months post-transplant, the patient developed biopsy-confirmed acute cutaneous GvHD that was treated with prednisone 30 mg/day and which she continued to require for recurrent skin flares. Voriconazole was initiated empirically three months post-transplant for pulmonary nodules identified on computed tomography (CT) scan. Three months later, the voriconazole dosage was increased from 125 mg twice daily to 175 mg twice daily after new pulmonary nodules were identified.

At the time of her NIH evaluation, patchy macular erythema and extensive macular pigmentation (solar lentigines) were noted on photoexposed areas of the body **(**Figure 2). These findings were consistent with chronic photodamage. Two weeks following replacement of voriconazole with posaconazole and institution of strict photoprotection, the erythema on photoexposed skin surfaces had faded to a light pink.

Patient 3 was a 40 year-old female with relapsed mediastinal, large B-cell lymphoma resistant to chemotherapy and radiation, who underwent a matched non-myeloablative alloPBHCT. The patient developed acute skin GvHD on day +44 and progressive, treatment-resistant sclerotic

skin manifestations of cGvHD 15 months post-transplant. Voriconazole was instituted three years prior to the patient's initial visit following pulmonary aspergillosis.

Six years, five months post-transplant, the patient presented to the NIH with new bullae on brightly erythematous and edematous sun-exposed areas of the upper and lower extremities as well as the V-area of the neck. Three days prior to presentation, she spent several hours at a picnic, reportedly primarily under the shade of a tree. Vesicles, bullae, and papules were noted on her hands and extensor forearms that evening **(**Figure 3A). A 3 mm punch biopsy taken from the left hand demonstrated epidermal necrosis most consistent with a phototoxic drug reaction **(**Figure 3B). The patient experienced marked improvement in erythema of photoexposed skin after switching from voriconazole to posaconazole and strict photoprotection, but she continued to have erythematous and erosive skin disease in the photoprotected areas, including her abdomen and back. The prednisone dosage was increased to 60 mg daily and the patient received rituximab weekly for four weeks in an attempt to control the GvHD. Three months later, she died of pseudomonal sepsis.

Patient 4 was a 47 year-old male who underwent a matched related nonmyeloablative alloPBHCT for chronic myelogenous leukemia (CML). One month post-transplant, the patient developed acute cutaneous GvHD. Similar eruptions recurred over his torso for the next several years. Thirty-one months post-transplant, voriconazole was initiated for a presumed pulmonary aspergillosis. Three months later the patient presented to the NIH with an 8-week history of coarse, erythematous to violaceous scaly, thickened skin on his cheeks and posterior and lateral neck **(**Figure 4). A 3 mm biopsy from the neck was suggestive of cutaneous lupus. The anti-nuclear antibody (ANA) titer was 5.4EU (0.0–0.9). Anti-ENA screen and anti-ds DNA titers were negative. Voriconazole-induced phototoxicity was diagnosed and the patient's antifungal treatment was changed to itraconazole. Four months later, the skin erosions had resolved and the violaceous discoloration improved significantly.

Patient 5 was a 59 year-old male with myeloid metaplasia and myelofibrosis who underwent a matched nonmyeloablative alloPBHCT and presented to the NIH nine months post-transplantation. Additionally, four months post-transplantation the patient developed biopsy proven hepatic GvHD. The following month voriconazole was initiated for a presumed pulmonary fungal infection. At the time of his evaluation, the patient reported a 6-week history of asymptomatic scaly plaques on sun exposed areas of the arms, neck, scalp, and v-neck area of the upper chest **(**Figure 5A). He described a recent increase in outdoor activity following recovery from his pulmonary infection. Biopsy from the left arm showed destruction of the basal epidermal layer with necrotic keratinocytes, compatible with a diagnosis of GvHD or phototoxic drug reaction **(**Figure 5C). Although this patient had received voriconazole episodically in the ensuing few months, the rash continued to improve **(**Figure 5B) with the institution of strict photoprotection.

Discussion

Drug-induced photosensitivity may be photoallergic or phototoxic. Phototoxic reactions do not require prior exposure and are dependent both on the dose of drug and ultraviolet light (UVL) exposure. Thus, a high dose of a photosensitizing medication combined with prolonged and or intense UVL exposure may result in erythema and edema resembling acute sunburn [6]. Repeated UVL exposure in patients on a photosensitizing drug can simulate the effect of chronic actinic damage with development of hyperpigmentation, dry skin, and solar lentigines. Phototoxicity occurs when the appropriate wavelength of light penetrates the skin where the photosensitizing drug or its metabolite is located. The photosensitizer absorbs the UVL energy, inducing oxygen radical formation, followed by cellular damage and an inflammatory response [7]. Pseudo-PCT represents a severe form of phototoxicity with bullae formation resembling

PCT without associated elevated blood porphyrin levels **(Patient 1)**. Voriconazole is a known phototoxic agent [8–17] and it has also been reported to induce pseudo-PCT [18–21].

In the five patients described, the diagnosis of phototoxicity was confounded by a history of cutaneous cGvHD and the inability to reliably distinguish between cGvHD and phototoxicity based on routine histological methods. We based the diagnosis of voriconazole-induced phototoxicity on a number of clinical features, including distinct photodistribution of skin lesions, a history of UVL exposure contemporaneous with drug administration, the absence of signs of reactivation of GvHD in other organ systems, and improvement of skin lesions upon discontinuation of voricaonazole and/or institution of strict photoprotection. Although biopsies were performed in 3 cases, the histopathologic findings of phototoxicity, including necrotic or apoptotic keratinocytes in various layers of the epidermis, vacuolization of the cells in the basal layer, and a mild superficial perivascular lymphohistiocytic infiltrate may also be observed in exanthematous GvHD. Similarly, the presence of epidermal necrosis is reflected in the severity of both GvHD and phototoxicity and cannot definitely separate either disease process [22–24]. Even the presence of eosinophils in the dermal infiltrate, a frequent finding in cutaneous drug reactions, does not reliably distinguish between phototoxic drug reactions and GvHD [22,25]. As exacerbations of cutaneous cGvHD may be triggered by both phototoxic and non-phototoxic drug eruptions, careful monitoring for persistent skin symptoms is warranted following identification and discontinuation of the causative agent.

Although voriconazole has been available for a number of years and is frequently used for prophylaxis [4], it is not yet approved for this indication. Posaconazole, a recently approved orally bioavailable antifungal, has been shown to prevent invasive aspergillosis in patients at high risk for infection, including patients with severe acute or chronic GvHD on treatment with corticosteroids [26]. Posaconazole has proven to be effective in patients with systemic mycosis refractory to voriconazole or who develop intolerable side effects with voriconazole [27]. It has broad-spectrum activity against *Candida*, *Aspergillus*, and *Zygomycetes* species [28,29]. Posaconazole-associated photosensitivity has not been described in the literature and we have not observed it in our cGvHD patients.

In our experience, the incidence of phototoxicity associated with voriconazole in the post-HCT setting is significantly higher than that reported in the initial clinical trial data. Whereas the initial voriconazole clinical trials enrolled hospitalized patients, our NIH population consisted primarily of outpatients with greater opportunity for exposure to UVL.

Because UVL exposure may induce a flare of cutaneous cGvHD independent of concurrent phototoxic drug exposure [30,31], sun avoidance and photoprotection are recommended for all patients evaluated in our cGvHD clinic. Furthermore, patients with cGvHD are often exposed to other potential photosensitizing agents in addition to voriconazole, including trimethoprim/sulfamethosazole, hydrochlorthiazide, and furosemide. Specific recommendations include sun avoidance at peak hours, use of protective clothing, and liberal application of both physical and chemical sunblocks that absorb both UV-A and UV-B radiation. Laundry rinse-cycle additives are also available in order to increase the UV protective factor of clothing [30].

Although the exact incidence of cutaneous drug reactions (CDR) is difficult to quantify, they are among the most frequent adverse drug reactions, accounting for approximately 10–20% of all reported adverse events. CDRs are most consistently associated with exposure to antimicrobial agents, including sulfonamides, flouroquinolones, penicillins, and cephalosporins [32,33]. The most common CDR is a morbilliform rash, characterized by fine pink macules and papules on the trunk which eventually coalesce and spread to the extremities. Skin lesions typically begin 1–2 weeks following drug exposure and fade slowly following

discontinuation. By contrast, urticarial hypersensitivity reactions usually develop within 1–2 days of drug initiation, and individual lesions resolve within 24 hours. The most worrisome CDRs are erythema multiforme/Stevens-Johnson syndrome/toxic epidermal necrolysis, a spectrum of severe drug hypersensitivity with variable skin involvement ranging from localized dusky targetoid plaques to widespread skin sloughing with mucosal membrane involvement and significant associated mortality. Often symptoms of a severe CDR do not present until several weeks after initial drug exposure [34].

Attention to the details of the clinical presentation and the drug administration history are of utmost importance in establishing the correct diagnosis in patients with cGvHD, given their complex medical history and the high likelihood of polypharmacy. In this setting, when confronted with a new onset eruption that is not considered diagnostic of cGvHD based on NIH consensus criteria [35], helpful clinical criteria in defining a CDR include: 1) exclusion of other causes for the eruption, such as viral exanthem; 2) identification of a temporal relationship between drug use and onset of the rash 3) improvement following drug cessation; and reactivation of the rash should upon rechallenge (if performed) [36].

As voriconazole has become a frequent choice for antifungal prophylaxis and treatment in the setting of alloHCT, the possibility of voriconazole-induced phototoxicity should be considered in all new skin eruptions, even those that simulate a flare of cutaneous cGvHD in patients with known cutaneous cGvHD. The recognition of voriconazole phototoxicity is especially important as efficacious treatment alternatives are readily available, and accurate diagnosis of phototoxic drug reaction will prevent misdiagnosis of cGvHD and unnecessary immunosuppression.

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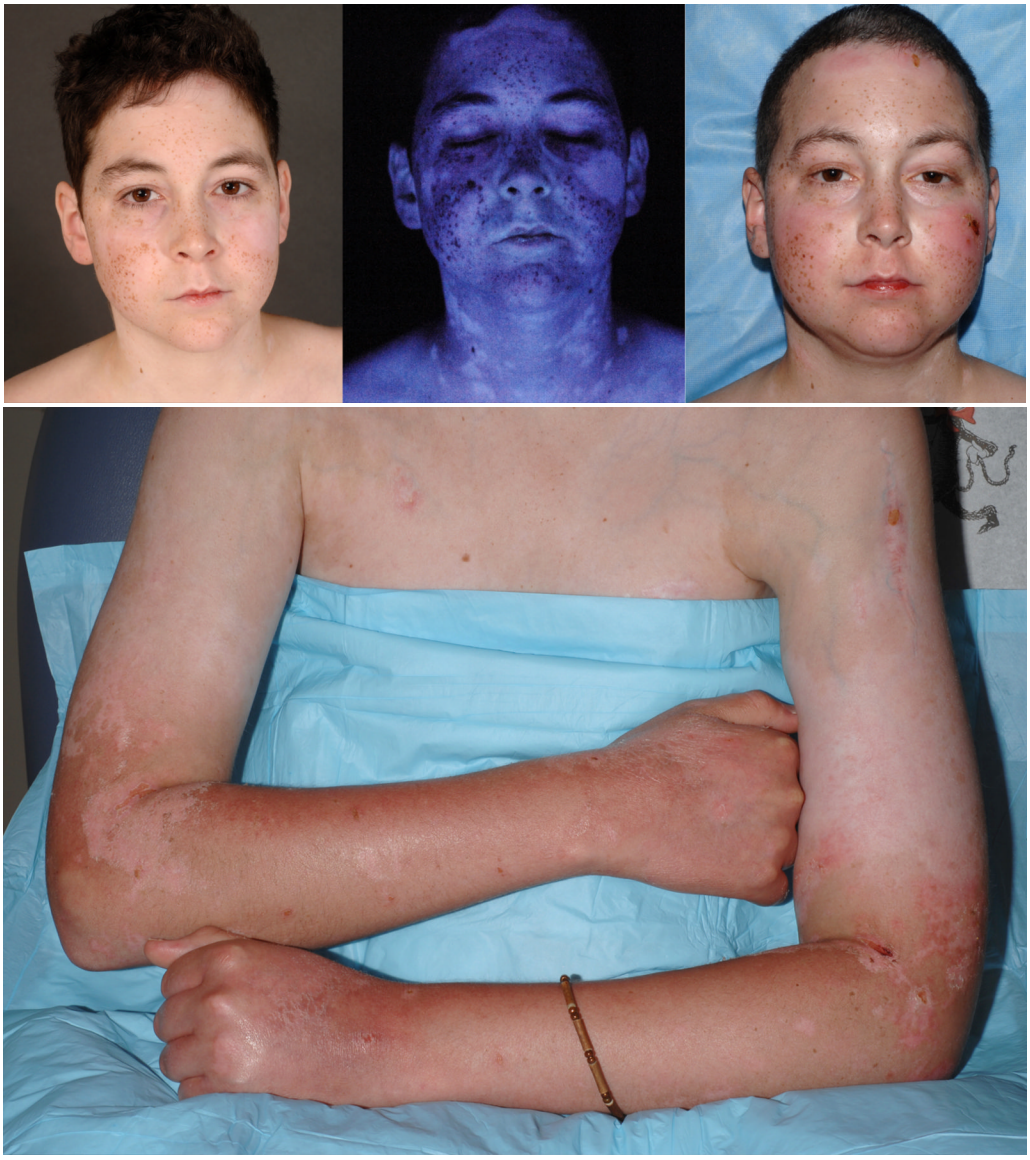
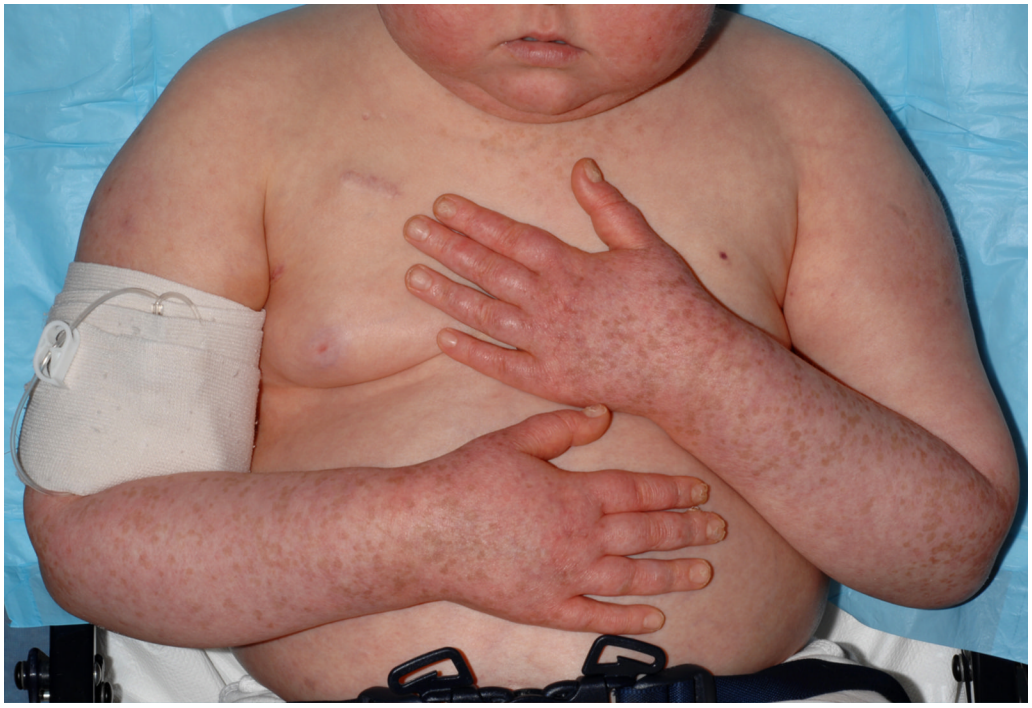


Figure 1.
Patient 1 prior to voriconazole administration (A,B) and after treatment with eight weeks of voriconazole 200mg BID (C,D). Multiple depigmented patches are present on the head and neck area (A) and accentuate upon visualization with Wood's lamp (B), consistent with vitiligo; (C) erythema and denuded bullae are present on the forehead, bilateral cheeks, nose, and chin; skin changes are most pronounced at sites of previous depigmentation; (D) prominent erythema on the photoexposed surfaces of the forearms and distal arms with superficial sunburn-like desquamation.



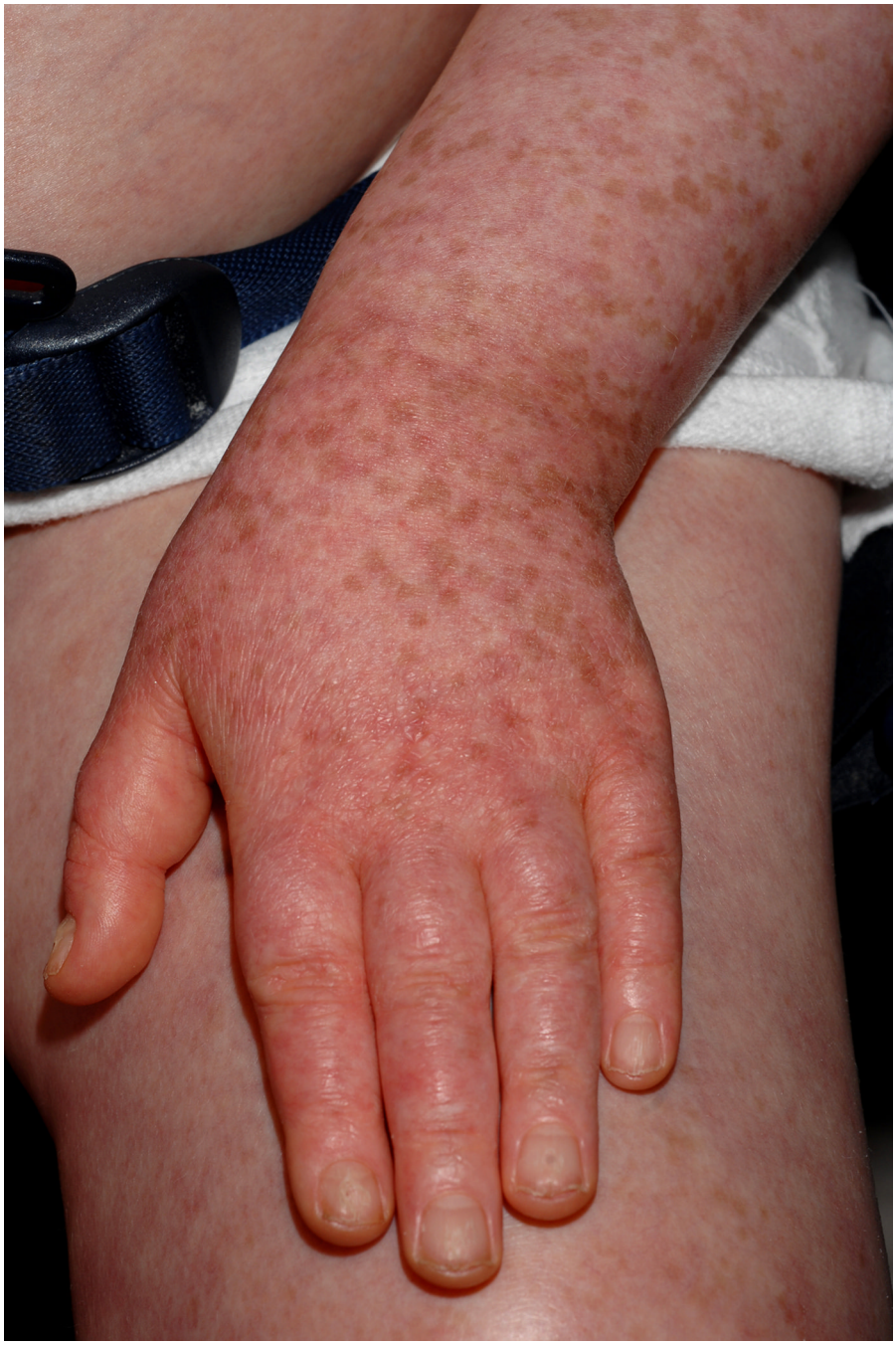
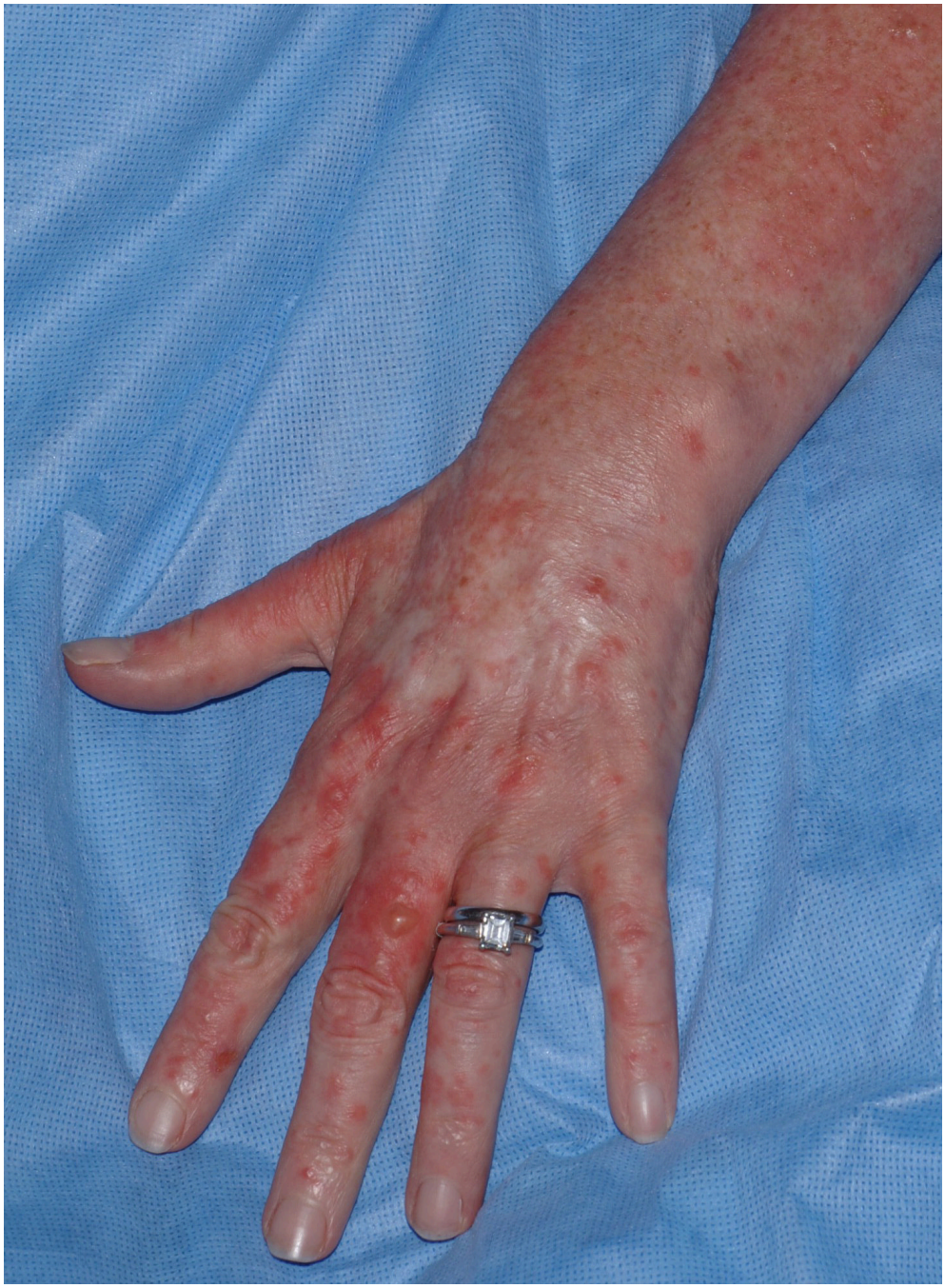


Figure 2.
Patient 2 following eleven months treatment with voriconazole 175mg BID. Erythema and multiple round tan/brown macules on the dorsal surfaces of the hands and forearms suggestive of ongoing phototoxicity and chronic photodamage, respectively. Similar erythema and macular pigmentation is present on the upper chest.



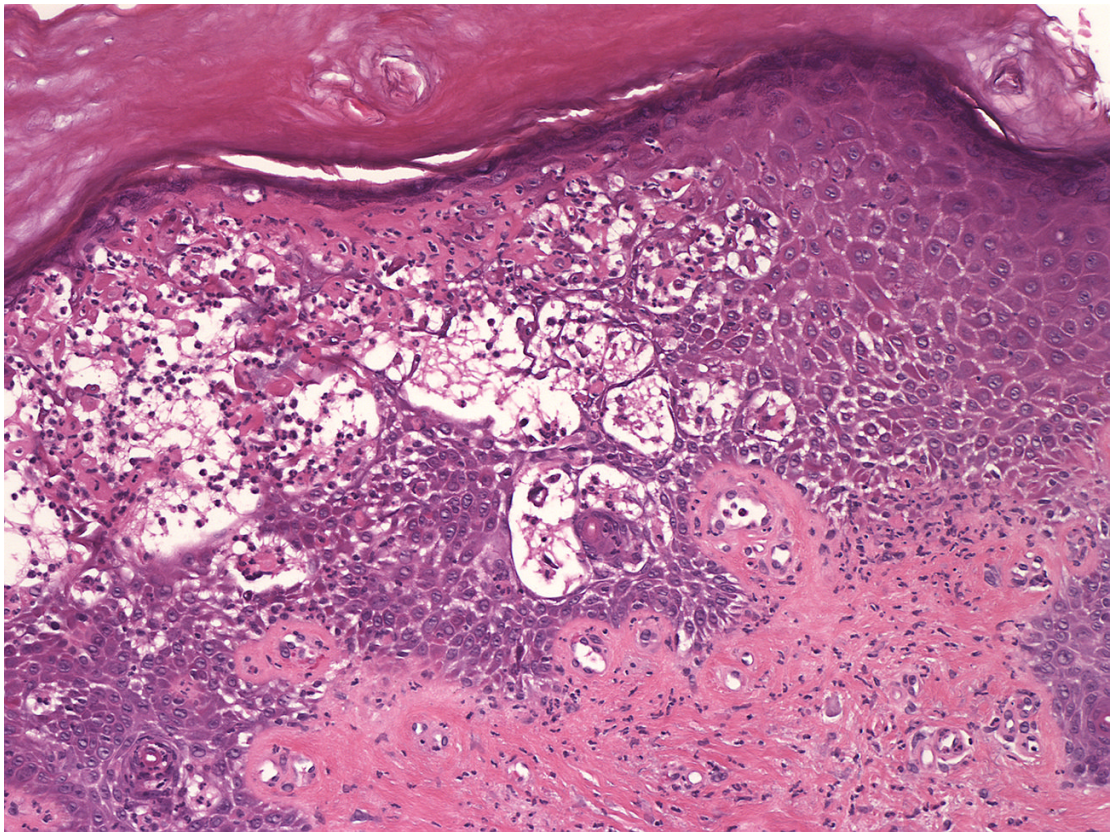


Figure 3.
A) Patient 3 following 36 months of voriconazole 200mg BID. The patient had ongoing cGvHD of the skin with erythema and sclerosis, but developed acute exacerbation of erythema with new intact bullae formation after sun exposure; B) skin biopsy demonstrates epidermal necrosis at all levels associated with a moderately dense neutrophilic infiltrate (hematoxylin and eosin, 10x magnification).

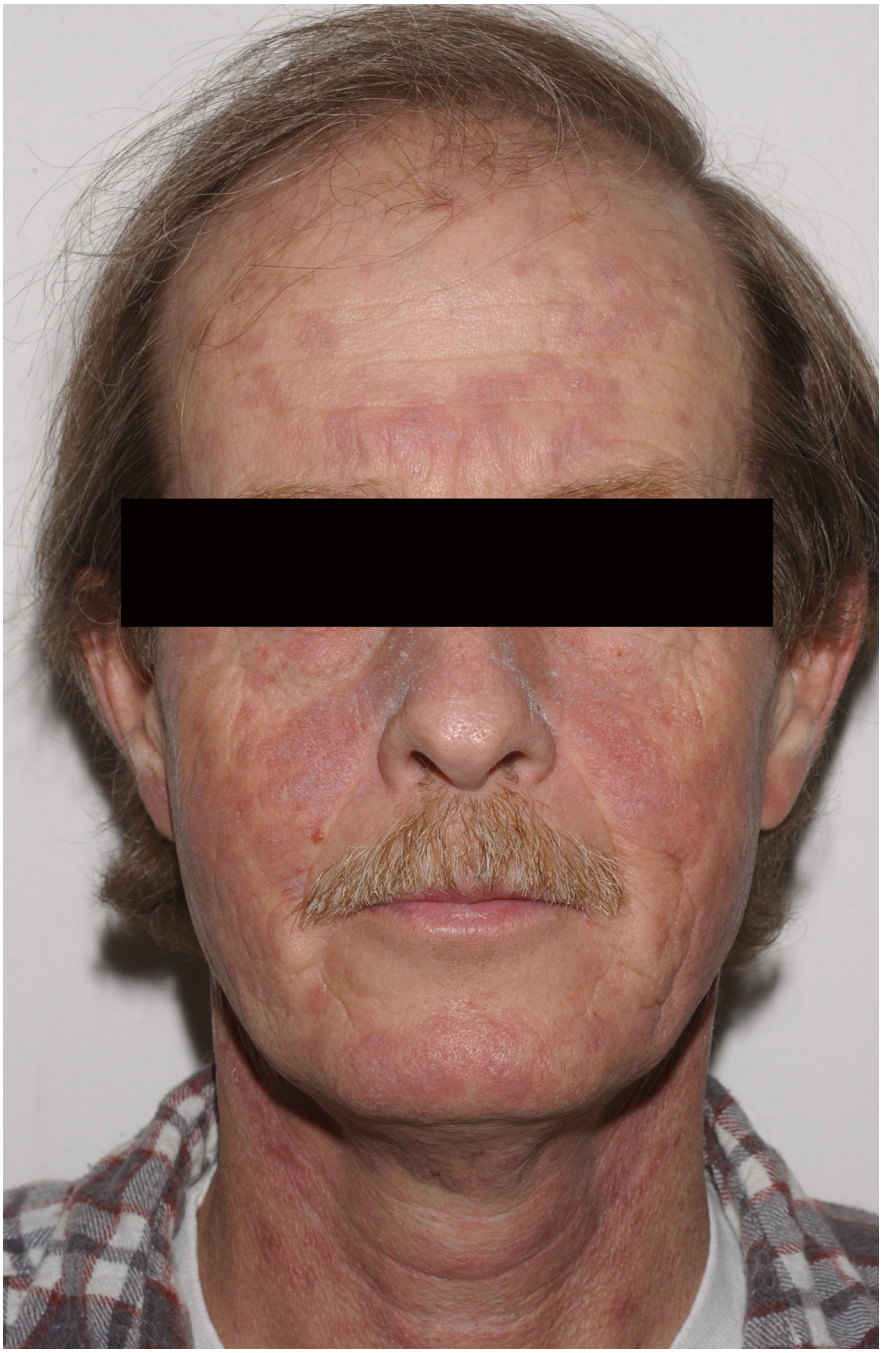
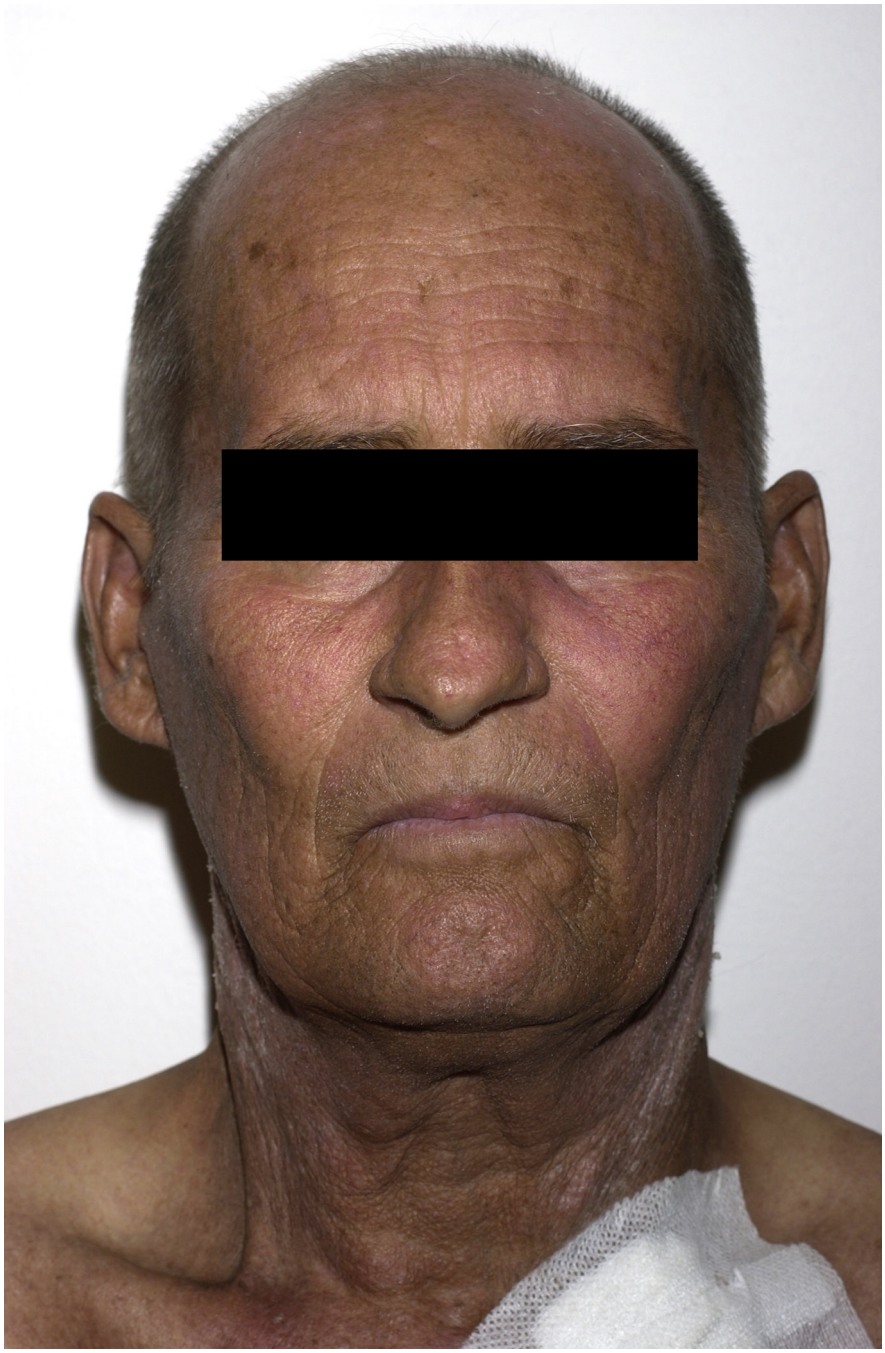
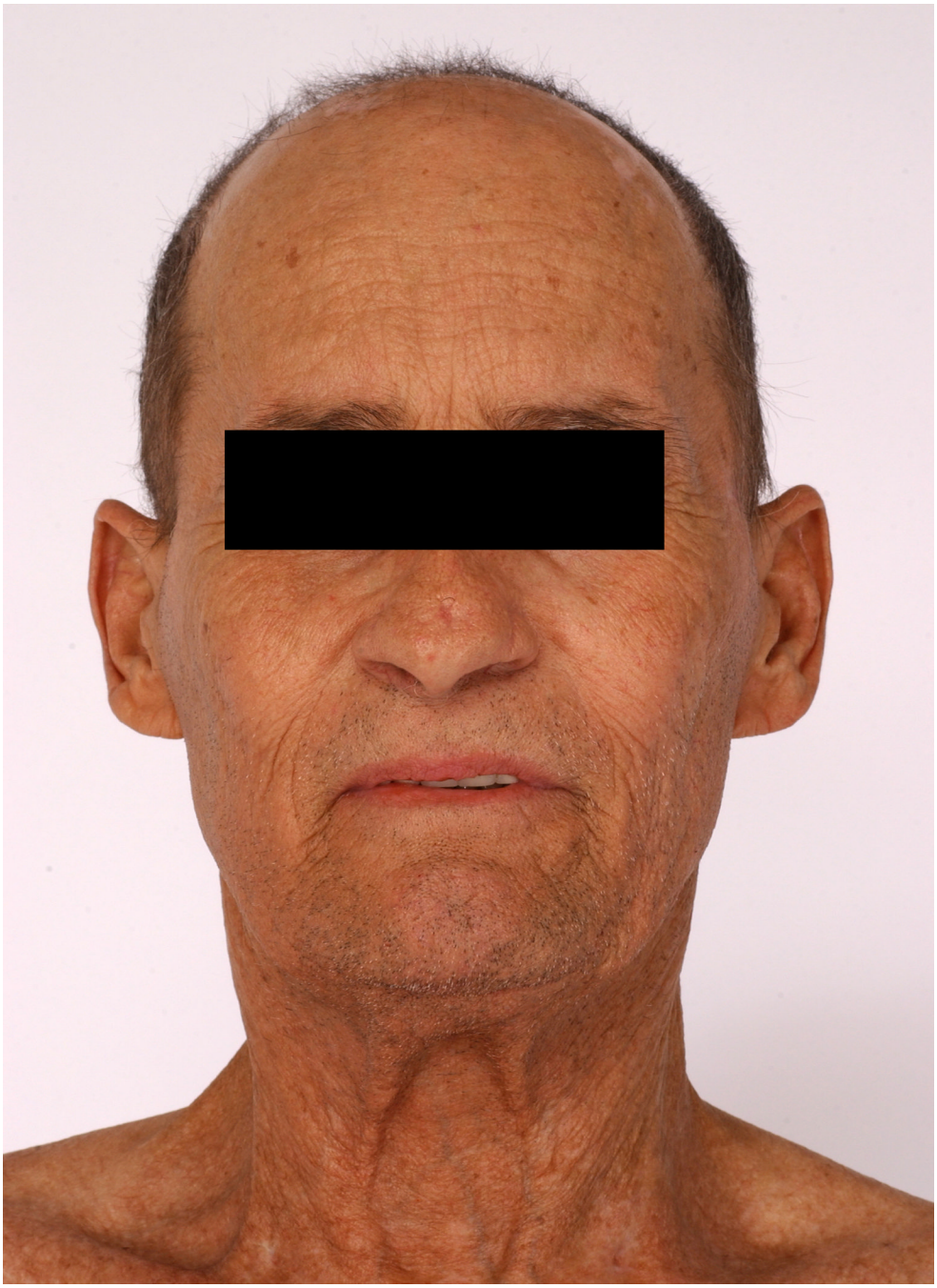


Figure 4.
Patient 4 following 3 months of treatment with voriconazole 200mg BID. Numerous erythematous/violaceous plaques on the face.





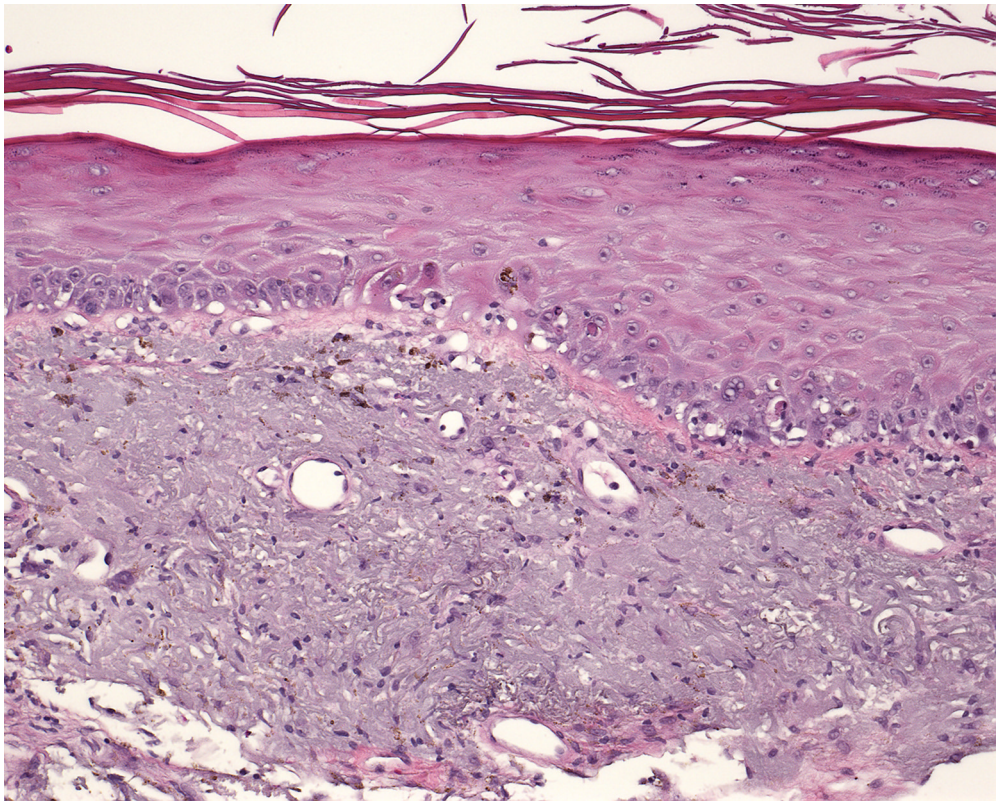


Figure 5.

A) Patient 5 following four months treatment with voriconazole 200mg BID. Marked hyperpigmentation on the photoexposed surfaces of the face; B) pigmentation is significantly improved one year later; C) pathology demonstrated hyperkeratosis, acanthosis, destruction of the basal epidermal layer with necrotic keratinocytes, and a sparse lymphocytic infiltrate with frequent pigmented macrophages (hematoxylin and eosin, magnification 10x).

Table 1

Patient characteristics

e/Sex	Primary disease	Hx acute skin GvHD	Hx chronic skin GvHD	cGvHD of other organ systems	Voriconazole dose	Latency between voriconazole initiation and phototoxicity	Concurrent potentially photosensitizing drugs	cGVHD therapy at time of phototoxicity diagnosis	Resolution of phototoxicity
M	Alveolar rhabdomyosarcoma	Yes	Yes	Oral	200mg BID	2 weeks	None	Prednisone 8mg QD	3 weeks
	Pre-B cell ALL	Yes	Yes	None	175mg BID	6 months	HCTZ	Prednisone 25mg BID Tacrolimus 0.5mg QAM, 0.25 QPM MMF 750mg q12hr Hydrocortisone 2.5% BID (face) Fluocinolone 0.1% BID (body)	2 weeks
F	Large B-cell lymphoma	Yes	Yes	Ocular Oral Hepatic	200mg BID	42 months	Amitriptyline	Extracorporeal photopheresis Prednisone 40mg QD Fluocinolone solution (scalp) Clobetasol ointment 0.05% (body) Tacrolimus ointment (face)	Improved in3 days, continued cGvHD flare
M	CML	Yes	Yes	Ocular Hepatic Pulmonary	200mg BID	1 month	None	Prednisone 50mg QOD MMF 1gm q12hr	4 months
M	Myeloid metaplasia/myelofibrosis	No	No	Ocular Hepatic Pulmonary	200mg BID	3 months	Lisinopril Furosemide	Prednisone 20mg QOD	3 months

acute lymphoblastic leukemia; CML, chronic myelogenous leukemia; HCTZ, hydrochlorothiazide; MMF, mycophenolate mofetil

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