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DERMATOLOGY GRAND ROUNDS AT THE NIH:

Recurrent erythematous plaques on sun-exposed sites in an African American boy with chronic granulomatous disease

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CASE SUMMARY

History

A 6-year-old African American boy with X-linked chronic granulomatous disease (CGD) presented with a two week history of progressive, erythematous facial plaques.

The patient had taken oral voriconazole for 5 months for a fungal pneumonia. Two months prior to evaluation, the voriconazole dose was increased from 7 mg/kg to 9 mg/kg twice daily. The patient's mother deferred a skin biopsy, and fluocinolone 0.025% ointment twice a day was prescribed along with strict sun protection measures. Eventually, the lesions resolved after voriconazole was discontinued. The patient returned 7 months later with a similar facial eruption that recurred after voriconzole was reinitiated at 9.3 mg/kg twice daily. The skin lesions progressed despite treatment with fluocinolone 0.025% ointment. His other medications were micafungin 45 mg intravenous daily and trimethoprim-sulfamethoxazole (TMP-SMX) 300 mg/60 mg by mouth twice a day.

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Conflicts of Interest Disclosure: None declared

Physical Examination

The patient was a well-developed boy with Fitzpatrick skin phototype V. Multiple erythematous oval plaques with irregular, elevated scaly pink borders were present on the forehead, central cheeks, and nose, most with violaceous centers (**Fig 1A**).

Histopathology

A punch biopsy of lesional skin revealed a superficial and deep perivascular lymphocytic infiltrate (**Fig 2A**). There was hyperparakeratosis, basal vacuolar changes, and scattered necrotic keratinocytes in the epidermis and along the basal layers of follicular infundibulum (**Fig 2B**). Alcian blue stain demonstrated abundant mucin in the reticular dermis (**Fig 2C**). PAS-D stain highlighted a thickened epidermal basement membrane (**Fig 2D**).

Significant Diagnostic Studies

A potassium hydroxide preparation of skin scrapings was negative for fungal elements. Laboratory studies revealed a positive antinuclear antibody (ANA) of 2.3 EU (reference range 0-0.9 EU). Anti-dsDNA was negative.

Diagnosis

Voriconazole-induced discoid lupus erythematosus (DLE)-like lesions in the setting of chronic granulomatous disease.

FOLLOW-UP

Voriconazole was discontinued a second time, and posaconazole was initiated for antifungal coverage. After one month, the lesions had significantly improved (**Fig 1B**). Interestingly, the patient's mother, a carrier of X-linked CGD, had a chronic palmar rash that was subsequently biopsied demonstrating lupus-like histology. Her ANA, anti-ENA, and anti-histone antibodies were negative.

DISCUSSION

CGD is an immunodeficiency resulting from a defect in the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase complex responsible for generating reactive oxygen species after pathogen phagocytosis. Impaired phagocytosis results in increased susceptibility to catalase-positive bacteria and fungi.[1]

Voriconazole is a second-generation triazole commonly used for antifungal prophylaxis in CGD patients and is indicated for invasive aspergillosis and other serious fungal or *Candida* infections.[2] It is fungicidal by inhibiting 13-α-sterol demethylase.[2,3]

Adverse effects of voriconazole include visual disturbances (21%), transaminase elevation (12.4%), and skin rash (7%), including photosensitivity.[3] In initial clinical trials, photosensitivity was reported in 1-2% of patients on long-term voriconazole. Subsequent reports have described numerous photosensitive reactions including pseudoporphyria,[4] photoaging,[5] facial erythema, cheilitis,[6-9] DLE-like lesions,[7,10-11] and multiple lentigines.[5,12-14] In addition, actinic keratoses, squamous cell carcinomas, [12,15] and

melanoma in situ[13] have been reported in patients on long-term voriconazole therapy. Product labeling now recommends discontinuing voriconazole if skin cancer develops.[3]

The mechanism of voriconazole-induced photosensitivity is unclear. Although the drug itself does not absorb UVA or UVB radiation, it has been postulated that the drug's principal metabolite, N-oxide, could be responsible for its phototoxic effects. However, *in vitro* absorption spectra of N-oxide voriconazole suggest absorption in the UVB range,[22] whereas broadband, predominantly UVA-mediated, photosensitivity is associated with voriconazole *in vivo*.[6]

Voriconazole-induced photosensitivity is well documented in the CGD population.[9-11,13,15-17,24] However, TMP-SMX, another photosensitizing drug, is also frequently used in CGD patients. It has been hypothesized that combining voriconazole and TMP-SMX may exacerbate photosensitivity.[17] Voriconazole is both a substrate and inhibitor of the P450 enzymes CYP2C19, CYP2C9, and CYP3A4. [2,3,8] As sulfamethoxazole inhibits CYP2C9 *in vitro*,[25] combining voriconazole with TMP-SMX could lead to elevated voriconazole levels and thus exacerbate photosensitity.[17] However, conflicting data exist regarding plasma voriconazole levels and photosensitivity reactions in children,[18-20] and specific toxic levels of voriconazole remain undefined. Further investigation is needed to determine the relationship between voriconazole metabolism and photosensitivity risk.

Lupus-like skin lesions have been reported in carriers of CGD and, less commonly, in patients with CGD.[10,11,26-36] ANA serologies in these patients are usually negative.[26-34] The pathogenesis of the lupus-like lesions is not fully understood. Decreased superoxide production in monocytes and neutrophils in CGD carriers correlates with the development of lupus-like skin lesions.[34] The abnormal respiratory burst results in delayed clearance of certain bacteria, fungi, and damaged cells. It has been hypothesized that impaired clearance of apoptotic cells could lead to chronic inflammation,[35,36] and these findings may be more pronounced in sun-exposed skin.[36] Alternatively, repeated antigen stimulation by nonphagocytosed organisms may theoretically lead to overproduction of autoantibodies. However, the frequently negative autoimmune serologies oppose this theory.[27,28]

Two prior cases of lupus-like eruptions associated with voriconazole have been reported in CGD patients.[10,11] A 10-month-old Caucasian child with CGD developed lupus-like lesions two months after starting voriconazole. The lesions resolved after discontinuing voriconazole.[10] A 28 month-old boy with CGD also developed lupus-like lesions one year after initiating TMP-SMX and voriconazole.[11] Our case confirms the association of lupus-like eruption and voriconazole treatment in patients with CGD by demonstrating lesion recurrence after drug rechallenge. In addition, together with prior reports,[14] this case illustrates that dark-skinned individuals are also susceptible to photosensitive reactions during voriconazole treatment.

It is unclear if voriconazole directly induces a lupus-like reaction in CGD patients or if the phototoxic effect of the drug unmasks an underlying predisposition to lupus-like lesions. Of note, one case of voriconazole-associated DLE-like lesions has been reported in an immunocompetent patient.[7] Although CGD patients are at higher risk of developing DLE-

like lesions, we believe the use of voriconazole in this setting may further increase the risk. Additional studies are needed to better define the association of lupus-like reactions in patients on voriconazole, including patients with CGD.

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ABBREVIATIONS

CGD	Chronic granulomatous disease
TMP-SMX	Trimethoprim-sulfamethoxazole
ANA	Antinuclear antibody
DLE	Discoid lupus erythematosus

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KEY TEACHING POINTS

- We report a case of a 6-year-old African American boy with X-linked chronic granulomatous disease (CGD) who developed discoid lupus erythematosus-like skin lesions after starting voriconazole.
- Voriconazole is commonly used to treat fungal infections in patients with CGD.
- Lupus erythematosus-like skin lesions have been reported in carriers of X-linked CGD and, less commonly, in patients with CGD.
- Voriconazole is a significant cause of drug-induced photosensitivity, and may play a role in unmasking an underlying predisposition to lupus-like skin lesions.
- Photoprotective measures and routine exams to monitor for skin toxicity, including skin cancer, are prudent during voriconazole treatment.

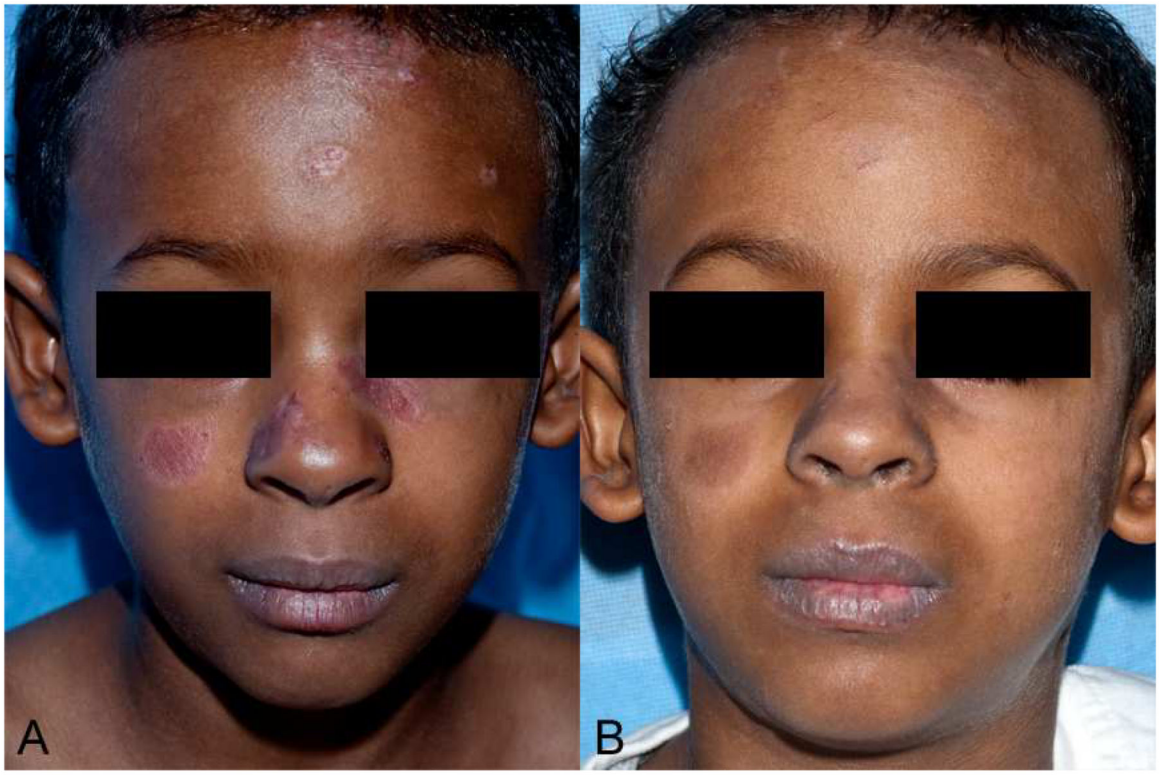

Fig 1. Discoid lupus erythematosus-like lesions in a patient with CGD following treatment with voriconazole

A, Multiple erythematous to violaceous plaques with irregular, elevated scaly pink borders on the forehead, central cheeks, and nose. **B**, Resolution of lesions with post-inflammatory pigment alteration 4 weeks after voriconazole was discontinued.

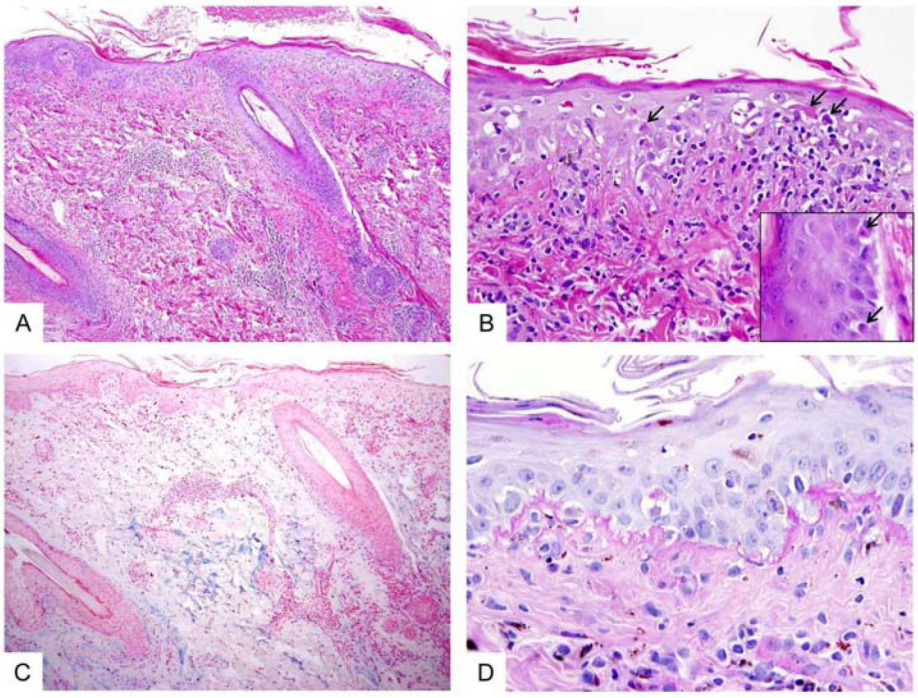

Fig 2. Histopathology of lupus-like lesions

A, Skin biopsy shows a mild perivascular chronic inflammatory infiltrate in the superficial and deep dermis. The overlying epidermis shows hyperparakeratosis and interface vacuolar changes. (H&E stain, original magnification = 100x). **B,** Higher magnification highlights frequent necrotic/dyskeratotic keratinocytes (arrows) in the epidermis and along the infundibular portions of hair follicles (inset). (H&E stain, original magnification = 400x; inset = 600x). **C,** An Alcian Blue stained section shows abundant mucin deposition in the reticular dermis. (Alcian blue stain, original magnification = 100x). **D,** PAS-D stained section shows irregularly thickened basement membrane along the dermal-epidermal junction. (PAS-D stain, original magnification = 600x)