Editorial

Fusarium Sepsis, Voriconazole, and the Skin

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In this issue of *Cutis*®, Bourgeois et al[1] report a neutropenic patient with disseminated *Fusarium* infection associated with toenail paronychia. Several aspects of this report are of interest to the dermatologist. First and foremost, it emphasizes the risk for fatal fungal sepsis originating from relatively minor fungal skin infections in patients with neutropenia. Cutaneous screening and treatment of chronic skin infections is important in patients who will be beginning chemotherapy or prolonged immunosuppression. Chronic fungal infections and gram-negative toe web infections can result in potentially fatal sepsis if they are not adequately addressed. Dermatologists should be aware of the most common pathogenic organisms and the risks associated with the newer drugs used to treat them. In particular, we need to be aware of the photosensitivity and risk for aggressive skin cancer related to voriconazole therapy.

Fusarium species and other nondermatophytic hyaline molds are common soil saprophytes that have emerged as important causes of sepsis in immunosuppressed patients. Among immunocompetent patients, *Fusarium* species may cause both onychomycosis and interdigital intertrigo,[2] which represents an important reservoir for sepsis during chemotherapy. Studies in the native Swiss population indicate that *Fusarium* species can be isolated from approximately 3% of patients with onychomycosis, and the fungus often fails to respond to standard therapy directed at dermatophytes.[3] On the basis of ribosomal DNA sequences, *Fusarium oxysporum* has been identified as the most frequently isolated species, accounting for approximately 54% of all isolates. *Fusarium proliferatum* and *Fusarium solani* account for 4% to 14% of cases of *Fusarium* nail infection. It is important to note that these species also are known to cause disseminated fusariosis in immunocompromised patients.[3]

Dermatologists use a wide variety of immunosuppressive agents to treat patients, and it is important to emphasize that despite the common occurrence of *Fusarium* in onychomycotic nails, there are insufficient data to support a recommendation for treatment of all onychomycotic nails before beginning immunosuppressive therapy. Patients with neutropenia are at greatest risk, and soft tissue infections such as paronychia or toe web infections are more frequent sources of risk for sepsis.

Fusarium species may cause septic arthritis, endophthalmitis, cystitis, osteomyelitis, and brain abscess. Disseminated infection should be suspected whenever 2 or more noncontiguous sites are involved. More than 80 cases of dissemination have been reported, usually in the setting of a hematologic malignancy with treatment-related neutropenia. Disseminated *Cylindrocarpon* (formerly *Fusarium) lichenicola* infection also has been reported to originate from nails and skin in the setting of neutropenia.[4] In addition to the skin, important portals of entry for disseminated infection include the respiratory and gastrointestinal tracts. Plumbing represents an important reservoir for *Fusarium* species and the organism often can be isolated from faucets, drains, and showerheads. Aerosolization of the fungus has been documented during showers and may represent a major source of respiratory infection.[5]

Skin lesions may help to establish the diagnosis of fungal sepsis. They commonly present as depressed black eschars with borders that are edematous and scalloped. Painful, red to violaceous plaques and nodules also may occur. The lesions usually are multiple and may involve the trunk, extremities, and genitalia. In a series of 6 patients with acute leukemia and disseminated *F solani* infection, necrotic skin lesions were present in 4 patients and periungual cellulitis in 2 patients.[6]

Treatment of *Fusarium* Infections

Fusarial onychomycosis may present as distal and lateral subungual onychomycosis, white superficial onychomycosis, and proximal subungual onychomycosis. The latter is most likely to be associated with leukonychia or periungual involvement. The condition often is refractory to treatment, though some patients may respond to itraconazole or terbinafine. Nail avulsion often is required.[7] Disseminated disease that occurs in patients with neutropenia or with

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deficient neutrophil or macrophage function is associated with mortality rates as high as 90%.[8]

While amphotericin has some activity against the fungus, many infections prove refractory to the older antifungal agents. Voriconazole is a newer agent that has demonstrated an excellent activity against a variety of systemic fungi including *Fusarium*. It may be a life-saving drug for patients with fungal sepsis and is increasingly being used for fungal prophylaxis. As a result, dermatologists will see patients treated with the agent and should be familiar with its cutaneous side effects.

Voriconazole is classified as a triazole antifungal drug and is approved by the US Food and Drug Administration for serious fungal infections caused by *Aspergillus*, *Fusarium*, *Pseudallescheria*, and *Scedosporium* species. The drug is associated with both photosensitivity and accelerated photoaging. It has been implicated as a cause of aggressive cutaneous squamous cell carcinomas (SCCs). Some young patients, including children, who have taken the drug for fungal prophylaxis develop a striking pattern of cutaneous photodamage and neoplasms reminiscent of xeroderma pigmentosum. Although SCC is the most common associated cutaneous malignancy, melanoma in situ also has been reported.[9-12]

Voriconazole also has been implicated in phototoxic reactions suggestive of porphyria cutanea tarda. Remarkable cheilitis may be seen in these patients, and some data suggest that the drug may impair endogenous retinoid metabolism. Although most patients have had porphyrin levels within reference range, true porphyria cutanea tarda also has been reported after the introduction of voriconazole.[13]

Conclusion

Fusarium species have emerged as an important cause of fungal sepsis in neutropenic patients. The organism commonly is found in showerheads and is aerosolized during showers. While the spread with showerheads represents the most important source of infection, chronic skin infections also have been implicated as a source of fatal fungal sepsis. Voriconazole has excellent activity against *Fusarium* and increasingly is being used for both treatment and prophylaxis. Dermatologists should be familiar with its potential to produce accelerated photoaging, aggressive SCC, melanoma, and porphyrialike presentations.

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