Successful treatment of *Aspergillus flavus* onychomycosis with oral itraconazole

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Systemic therapy with griseofulvin and ketoconazole has been used in onychomycosis resistant to topical agents, but because of a cure rate that remains suboptimal, especially in nondermatophyte and toenail infections, the search for more effective therapy has continued.

Case report. A 47-year-old woman had had a dystrophy of the left fourth fingernail for at least 1 year. Examination revealed distal onycholysis, and marked subungual hyperkeratosis of the distal third of the digit (Fig. 1). Radiographs were unremarkable. Initial cultures grew only *Candida* organisms. Topical and oral ketoconazole treatment (200 mg once daily for 5 months) and laser destruction of the nail plate were unsuccessful.

On reevaluation, a KOH preparation suggested the presence of *Aspergillus* species. Cultures on Sabouraud and fungal synthetic amino acid media, which do not inhibit saprophytes, grew brown-black colonies identified as *Aspergillus flavus*, sensitive to itraconazole. Whitfield's ointment (benzoic and salicylic acids), twice daily for several months, was ineffective, and therefore oral itraconazole, 100 mg/day, was begun.

During the 5 months of oral itraconazole treatment, no adverse effects were recognized. Improvement in nail dystrophy was noted within 1 month, with the regrowth of approximately 1.5 mm of nail plate. At 4 months almost all the nail plate was normal (Fig. 2), and repeated KOH preparations and cultures, which had been positive during most of the treatment, were negative.

Discussion. Recently a class of agents called azoles, administered systemically and topically, have been used in the treatment of a variety of deep and superficial fungal infections. Use of the azoles should be considered in patients with fungal organisms sensitive to the particular azole, who meet any of the following criteria: (1) griseofulvin resistance, (2) griseofulvin nonresponsiveness, (3) griseofulvin intolerance, or (4) griseofulvin drug interaction. Ketoconazole, an imidazole, is one of the second-generation azoles. As with other imidazoles, ketoconazole is active against all the main superficial fungal pathogens. However, its activity against *Aspergillus* species is poor.

Itraconazole inhibits fungal sterol synthesis principally through interference with cytochrome P-450 enzymes. It is highly lipophilic and has shown activity against a
number of fungal species, including *Aspergillus fumigatus*. With a half-life of 1.5 hours, itraconazole has 24-hour minimum inhibitory concentrations similar to those of amphotericin B and higher than ketoconazole after oral administration. Variations in blood levels have been reported and have been attributed to induction of an enzyme active against the drug in certain genetically predisposed persons. When taken orally, serum levels are not affected by food. Excretion is mostly fecal (>85%), with a small urinary component. It does not appear to interact with anticoagulants, rifampin, or cyclosporine in animal studies.

Several studies have been undertaken to assess the usefulness of itraconazole in superficial mycoses. In a study of more than 1000 patients with mycoses, some involving the skin, it was determined that 100 mg of itraconazole administered daily for 14 days was effective for tinea corporis or tinea cruris; 100 mg/day for 30 days was effective for tinea pedis or tinea manuum. Further, in a randomized double-blind study that compared 100 mg/day of itraconazole with 500 mg/day of griseofulvin (unknown formulation), itraconazole was found to be at least as effective as griseofulvin. When used in the treatment of chronic and recurrent dermatophytoses, a regimen of 100 mg/day was found to be superior to 50 mg/day dosing in time until response, although there was no significant difference in response rate.

Itraconazole appears to be well tolerated. In a study of 185 patients given 50 or 100 mg/day, only five reported adverse reactions. These reactions were mild and included headache, vomiting, gastrointestinal complaints, pyrosis, and tachycardia. No liver enzyme or electrolyte abnormalities were noted. Other studies have confirmed a mild side effect profile.

The initial description of blastomycosis-like pyoderma has been attributed to De Azua and Sada y Pons, who in 1903 reported the case of a patient with vegetating skin lesions that resembled blastomycosis or tuberculosis cutis and had microscopic features of an epithelioma. Similar cases have been reported since then; all clinically resembled blastomycosis, tuberculosis, or a halogen eruption.

Numerous organisms, including *Staphylococcus aureus*, *β*-hemolytic streptococci, *Pseudomonas aeruginosa*, *Proteus* species, and *Escherichia coli*, have been cultured from these lesions; *S. aureus* is the most common. In 1957 these vegetative lesions were given the name "mycosis-like pyoderma" by Brown and Kligman. In 1979 Su et al. proposed criteria for the diagnosis of blastomycosis-like pyoderma based on an analysis of seven cases. These include the clinical presentation of large verrucous plaques with multiple pustules and elevated borders, the presence of pseudoeppitheliomatous hyperplasia with abscesses, the growth of at least one pathogenic bacterial species from culture of a tissue biopsy specimen with negative cultures for deep fungi and mycobacteria, negative fungal serologic findings, and a normal serum bromide level. The initial lesion of blastomycosis-like pyoderma usually develops at a site of trauma, and either local or systemic host compromise is believed to be important in the production of this chronic, vegetating tissue reaction to a superficial bacterial infection.

Numerous treatments for blastomycosis-like pyoderma have been attempted, including systemic antibiotics, curettage, topical antibiotics, and carbon dioxide laser debriement. Although various antibiotics have been used, including penicillin and minocycline, there have been no reported trials with ciprofloxacin. We present a patient with blastomycosis-like pyoderma culture-positive for *P. aeruginosa* who responded to ciprofloxacin.

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