Disseminated Cutaneous Sporotrichosis Treated With Itraconazole

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A 72-year-old Hispanic man with diabetes presented with a 4-week history of a tender nonhealing ulcer on the fifth digit of the left hand and a 3-day history of fever, chills, malaise, anorexia, and tender fluctuant nodules on the abdomen and left elbow. The patient, an avid gardener, was using prednisone and methotrexate for a debilitating seronegative polyarthropathy. A diagnosis of disseminated cutaneous sporotrichosis was made based on epidemiologic risk factors, clinical appearance, histopathologic examination, and a positive fungal culture. Use of prednisone was discontinued, the dosage of methotrexate was decreased, and use of oral itraconazole 400 mg/day was instituted. The patient's lesions cleared within 5 months, and no recurrence was noted during a 3-month follow-up. This case illustrates the typical association of the rare entity of disseminated cutaneous sporotrichosis with immunosuppression, an unusual lack of internal involvement, and a gratifying response to itraconazole.

Sporotrichosis is an infection caused by *Sporothrix schenckii*, a dimorphic fungus commonly found in the soil, on sphagnum moss, and on inanimate objects contaminated with soil or dust. Infection typically occurs through traumatic inoculation of the skin with contaminated organic material. Infection can remain localized but more often erupts as a lymphocutaneous disease extending along regional lymphatics. Disseminated sporotrichosis, which is rare, is most commonly associated with immunodeficiency.[1] Patients become infected via cutaneous inoculation or inhalation with subsequent hematogenous dissemination to the skin or other organ systems such as the lungs, joints, meninges, and bone.[2-9] We describe a case of disseminated cutaneous sporotrichosis in a patient who was immunosuppressed and who was successfully treated with oral itraconazole.

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Case Report

A 72-year-old Hispanic man presented with a 4-week history of a nonhealing lesion involving the fifth digit of the left hand and a 3-day history of fever, chills, anorexia, and additional skin lesions. The patient had diabetes and a debilitating seronegative polyarthropathy. Oral medications included glyburide 2.5 mg/day, prednisone 5 mg/day, and methotrexate 17.5 mg/week. An avid gardener, the patient often received traumatic abrasions.

The patient was febrile (102.2°F) but otherwise not in acute distress. He had a 3×1.2-cm tender ulceration of the fifth digit on the left hand (Figure 1); 8 erythematous, fluctuant, tender, deep nodules on the abdomen; 1 large fluctuant nodule on the left elbow; and left epitrochlear lymphadenopathy (Figure 2). Results of laboratory tests indicated leukocytosis (white blood cell count, 24,000/mm^2), mild anemia (hemoglobin level, 11.7 g/dL; hematocrit level, 35.3%), and elevated erythrocyte sedimentation rate (53 mm/h). Cultures from the finger ulceration (tissue) and the abdominal nodules (aspirate) were positive for *S schenckii*. Biopsy results from the finger lesion revealed a granulomatous infiltrate admixed with plasma cells; fungi were seen with use of hematoxylin and eosin stain. Results of chest radiographs were normal. Blood cultures were negative for bacteria and fungi. According to radiographs and bone scans, there was no osseous involvement.

The patient was diagnosed with disseminated cutaneous sporotrichosis. Treatment with oral itraconazole 400 mg/day was started, prednisone was discontinued, and the dosage of methotrexate was reduced to 7.5 mg/week. The patient became afebrile within 48 hours, all lesions resolved within

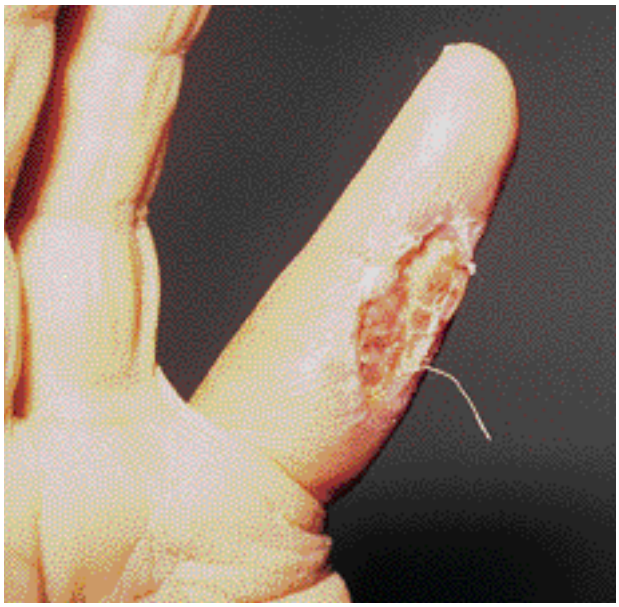

Figure 1. Primary inoculation site.

6 months, and there was no recurrence during a 3-month follow-up.

Comment

Dissemination is a rare manifestation of infection with *S schenckii*. A search of the readily available English literature identified 253 cases of disseminated sporotrichosis. There are 2 types of disseminated sporotrichosis—systemic and cutaneous. Usually, patients with systemic disease also have disseminated cutaneous lesions; however, fewer than 1% of patients with disseminated cutaneous lesions also have systemic involvement.[10] Patients with disseminated cutaneous involvement typically present with extensive disease in which lesions occur far from the initial inoculation site. Moreover, patients with disseminated skin lesions often have (and should be thoroughly checked for) internal involvement. Excluding our case, to our knowledge, only 10 cases of disseminated cutaneous sporotrichosis without internal disease have been reported.[3,11-14] Smith et al[15] reported only 1 of 3 cases of disseminated cutaneous disease limited to the skin. A case report by Kurosawa et al[16] involved a patient with the human immunodeficiency virus (HIV). However, this patient later developed systemic dissemination to the eye.

Disseminated sporotrichosis often is associated with immunodeficiency, the primary cause of which is impairment of the host's cell-mediated immunity.[17] Our patient was taking 2 immunosuppressive medications. He also had diabetes mellitus, which may have contributed to his decreased immune status. Other immunity-impairing conditions and practices associated with disseminated sporotrichosis include HIV infection, chronic alcohol abuse, diabetes mellitus, sarcoidosis, pulmonary tuberculosis, organ transplantation, hematologic and lymphoreticular malignancies, and long-term ingestion of high-dose steroids or other immunosuppressive medications.[8,15,16,18-25] If none of these conditions or practices is obvious in an individual with disseminated sporotrichosis, the patient should be checked for immunodeficiency.[26] To our knowledge, 3 cases of disseminated cutaneous disease in patients who were not immunodeficient have been reported.[3]

Amphotericin B has been the standard treatment for disseminated sporotrichosis.[1,27,28] Intravenous infusion usually is performed slowly (0.25 to 1.0 mg/kg/d–maximal dose for cure, 0.75–3.0 g). Although treatment usually is successful, the side effects often are intolerable. Treatment is discontinued mainly because of renal toxicity, fever, chills, hypokalemia, nausea, vomiting, or anemia.[1] Adding a medication to amphotericin B seems warranted in the treatment of disseminated sporotrichosis.[27,29]

Itraconazole is an effective therapy for infection with *S schenkii*.[30-37] In 1986, Restrepo et al[35] were the first to demonstrate its efficacy in treating primary lymphocutaneous disease. Edwards et al[6] reported that itraconazole might be the medication of choice for localized and regional sporotrichosis primarily because its side-effect profile is more favorable than that of other treatment modalities. Itraconazole produces minimal toxicity and is well tolerated by patients not infected with HIV, even at dosages as high as 400 mg/day over long periods.[38] When itraconazole is used in the management of localized lymphocutaneous sporotrichosis, response rates are excellent.[27]

The role of itraconazole in disseminated disease is less clear. A literature search identified 38 cases of itraconazole therapy for disseminated sporotrichosis. In these cases, itraconazole was primarily used for long-term maintenance after initial treatment with amphotericin B.[28] However, itraconazole also is efficacious as a primary therapeutic agent after failed treatment with amphotericin B.[18] Sharkey-Mathis et al[39] reported that 11 of 15 patients (73%) with osteoarticular sporotrichosis responded to itraconazole after failed therapy with amphotericin B, iodides, ketoconazole, and fluconazole, although 4 of the 11 later relapsed. Winn et al[40] reported on 6 patients with disseminated sporotrichosis. With these patients, amphotericin B treatment initially failed but then started working with the addition of itraconazole at the minimal dosage of 200 mg/day; average follow-up was 18 months. After results of in

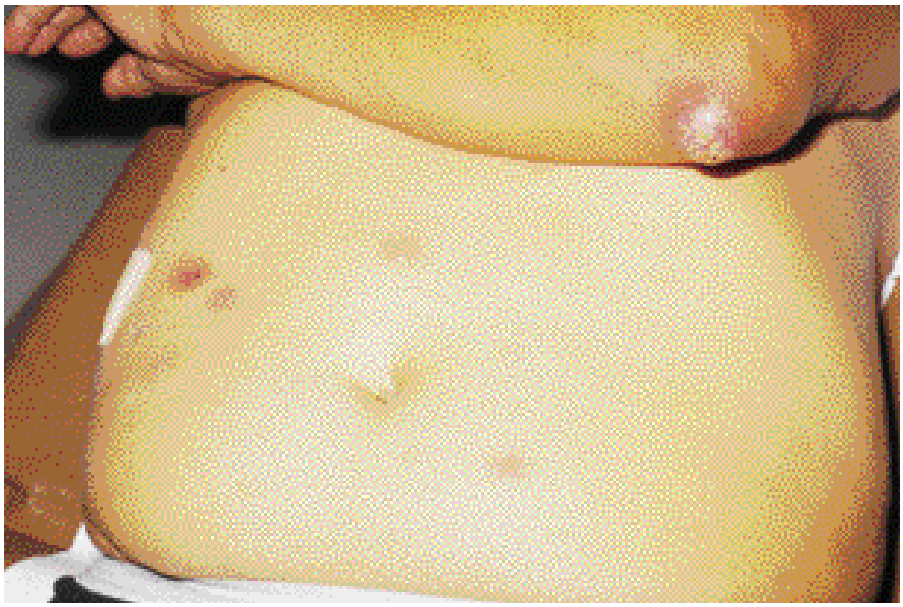

Figure 2. Multiple cutaneous nodules (disseminated disease).

vitro testing showed that *S schenckii* was resistant to amphotericin B, Baker et al[41] used itraconazole to successfully treat disseminated sporotrichosis and fungemia in an alcoholic patient with diabetes. Kauffman et al[42] used results from multicenter, nonrandomized, clinical trials, small retrospective series, and case reports to develop practice guidelines for managing sporotrichosis. For disseminated osteoarticular disease, they recommended itraconazole as a first-line therapy; for other disseminated cases, they cited amphotericin B as the preferred treatment and itraconazole as an acceptable alternative modality.

Using itraconazole to treat disseminated sporotrichosis in patients with HIV poses a greater challenge. Edwards et al[6] indicated that itraconazole seems to work better as a maintenance treatment for disseminated sporotrichosis in patients with acquired immunodeficiency syndrome (AIDS), especially when the medication is administered after amphotericin B. However, in treating disseminated sporotrichosis in a patient with HIV, Bolao et al[38] found that improvement occurred with itraconazole treatment after failed treatment with amphotericin B and other antifungal medications. Oscherwitz and Rinaldi,[20] treating disseminated sporotrichosis in a patient with HIV, reported successful management with itraconazole alone. According to the practice guidelines developed by Kauffman et al,[42] in patients coinfected with HIV, initial use of amphotericin B for the treatment of disseminated sporotrichosis should be followed by lifelong maintenance therapy with itraconazole.

To our knowledge, this is the first report of disseminated cutaneous sporotrichosis treated with itraconazole monotherapy. As itraconazole is successful in treating both localized and systemic sporotrichosis, its effectiveness in our patient's case is not surprising. Of the other 10 patients reported with disseminated cutaneous sporotrichosis: 4 were treated with amphotericin B[3,15]; one was treated with ketoconazole[13]; one was treated with itraconazole after developing renal toxicity to amphotericin B but died 8 days later[12]; one died before antifungal treatment was started[14]; and three reported no treatment.[11] After diagnosing disseminated cutaneous sporotrichosis in our patient, we discontinued his prednisone treatment and reduced his dosage of methotrexate. The resulting simple alteration in the degree of immunosuppression likely provided a boost in our patient's innate immune status and thereby contributed to the ease with which he was treated.

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