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Sporotrichosis

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Abstract Sporotrichosis is a deep fungal disease caused by a dimorphic fungus, *Sporothrix schenckii*. It occurs more frequently in the tropical and subtropical areas and is mainly characterized by nodular lesions of cutaneous and subcutaneous tissues and adjacent lymphatics that suppurate and ulcerate. Infection occurs by manipulation of contaminated soil, cats, or some wild animals or by inhalation of spores. Itraconazole is the best drug for treatment of sporotrichosis.

Definition and history

Sporotrichosis is the most common, and least severe, of the deep mycoses and is characterized by the subacute and chronic evolution of cutaneous or subcutaneous nodular lesions. It is caused by the traumatic inoculation of the fungus *Sporothrix schenckii* into the subcutaneous tissue through soiled wounds or by inhalation of spores via the upper respiratory tract. Zoonotic transmission from scratch injury or bites of cats or armadillos is also reported.[1-5]

The first report of sporotrichosis was published in the Johns Hopkins Hospital Bulletin in 1898 in Baltimore, USA. The patient, a 36-year-old man, was observed by medical student Benjamin Schenck, who reported multiple ascending, ulcerated nodules on the forearm proximal to a lesion on the right index finger. These lesions appeared after a puncture wound, and fungal organisms from the genus *Sporotrichum* were isolated.[6] Similar cases of subcutaneous abscess caused by fungus of the same genus were described by others[7,8]; in 1900, Hektoen and Perkins[8] described the morphology of the pathogen in detail and called it *Sporothrix schenckii*. In 1912, De Beurmann and Gougerot[9] published a complete treatise on the disease.

Etiological agent

Sporothrix schenckii is a ubiquitous environmental saprophyte that can be isolated from soil, wood, grain, land, and marine animals and even some insects. Professional activities associated with infection include gardening, carpentry, agriculture, animal husbandry, and veterinary practice.

Sporothrix schenckii is a dimorphic fungus, existing in hyphal form at temperatures below 37°C and as a yeast above 37°C.

The organism grows readily on Sabouraud dextrose agar at 25°C, producing lobulated, cream-colored, smooth or verrucous, moist colonies with occasional aerial mycelia. After a few days, it matures into a black leathery colony.

The organisms are difficult to find in the tissue when using simple tissue stains alone; therefore, if sporotrichosis

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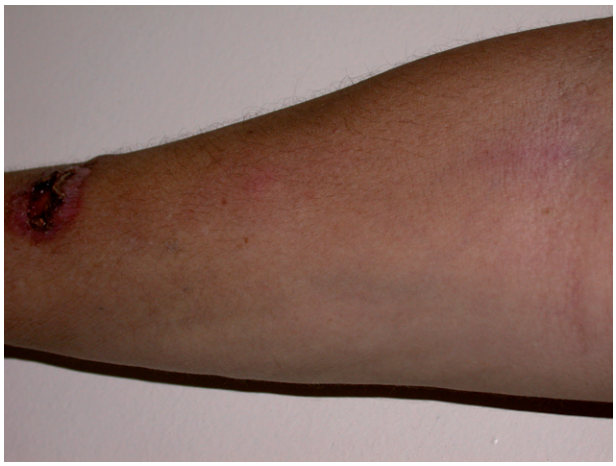

Fig. 1 Sporotrichosis with ascendant nodular lymphangitis of the right forearm.

is clinically suspected, it is necessary to perform fungal cultures and identification to confirm the diagnosis.[10-12]

Epidemiology and transmission

Sporotrichosis occurs worldwide, but it is more commonly seen in tropical and subtropical zone regions. It is endemic in Central and South America and in Africa.[13]

The largest known outbreak occurred between 1941 and 1944 in South Africa, where over 3000 cases were documented among gold miners in Witwatersrand. The epidemiology pointed to a wood source. The patients were treated with potassium iodide, and the wood and patients' clothing were treated with formaldehyde before the disease disappeared from the region.[14-17] In the United States, the largest recorded outbreak of sporotrichosis involved 84 patients in 15 different states that had handled conifer seedlings in 1988.[18-20]

Transmission occurs, in most cases, through traumatic inoculation of fungi through the skin and subcutaneous fat. Approximately 10% to 62% of patients relate infection to recent penetrating trauma with plant thorns, wood splinters, or contaminated organic material.[21] Typically, the patients are healthy young adults younger than 30 years. Zoonotic transmission can occur after being scratched or bitten by animals, especially cats, rodents, and armadillos.[1,5,22]

An outbreak of sporotrichosis related to the domestic and professional handling of cats was reported in Rio de Janeiro, Brazil, by Barros et al.[5] Of the 178 cases that were confirmed by culture between 1998 and 2001, 156 (88%) reported domestic or professional contact with cats. The findings led the authors to propose a revised at-risk subpopulation to include veterinary workers, animal carers, and cat owners.[5]

The high infectivity of cats was demonstrated by Schubach et al.[3,4] *Sporothrix schenckii* was also isolated from 100% of the cutaneous lesions taken from cats with feline sporotrichosis. *Sporothrix schenckii* was also isolated from the nasal cavity in 66.2%, from the oral cavity in 41.8%, and from the claws in 39.5% of the cats tested.[3,4] Conti-Diaz[1] found a prevalence of disseminated cutaneous sporotrichosis of 3.3% among armadillo hunters. A curious case linked to zoonotic transmission of cutaneous lymphatic sporotrichosis was reported after a 54-year-old man was bitten by a fire ant of the genus *Solenopsis*.[23]

Although less common, transmission may occur through inhalation of the fungus through the upper respiratory tract, with possible subsequent hematogenic dissemination. When inhaled, a picture of granulomatous pneumonitis with cavitation may arise that may mimic tuberculosis.

In 1970, Lynch recognized the role of *S schenckii* as an opportunist infection in immunocompromised individuals.[24] Alcoholism, diabetes mellitus, hematologic malignancy, chronic obstructive pulmonary disease, organ transplantation, and use of immunossupressive drugs, and, more recently, HIV infection predispose to acquisition of clinical sporotrichosis.

Clinical manifestations and differential diagnosis

Several clinical forms of sporotrichosis are observed according to the size of the infective inoculum, fungal virulence, depth of inoculation, and immunological state of the host.[22]

Sampaio and Lacaz[25] proposed classifying sporotrichosis into 4 clinical categories: (i) lymphocutaneous, (ii) fixed cutaneous, (iii) multifocal or disseminated, and (iv) extra-

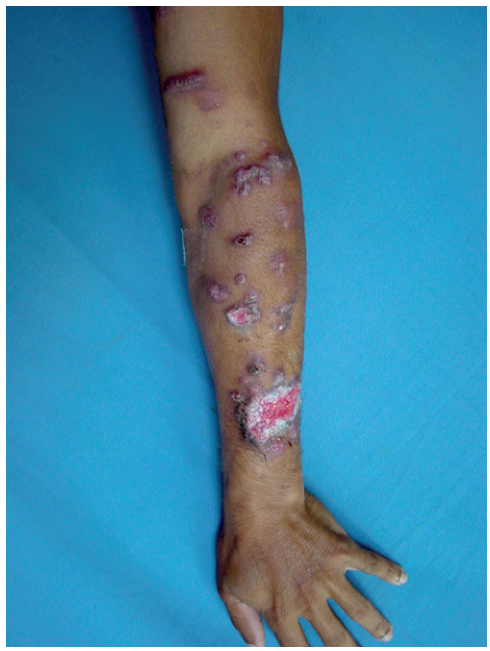

Fig. 2 Sporotrichosis of the left forearm showing ulceration and indurated nodules.

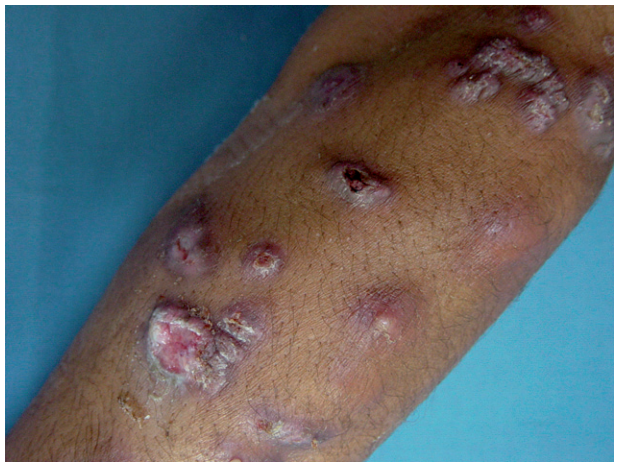

Fig. 3 Sporotrichosis of the left forearm showing ulceration and indurated nodules (same patient as in Figs. 2 and 4).

cutaneous, the latter usually being due to inhalation and hematogenic dissemination of the parasite. Lesions usually arise in the limbs, although in children, facial lesions are also common, being reported in up to 92% of pediatric cases. Cutaneous disseminated and systemic sporotrichosis are rare variants and are almost always associated to immunosuppression of the host.[21]

The lymphocutaneous form of the disease is the most frequent variant, representing over 75% of all cases.[21,22] It is characterized by the emergence of an indurated papule, approximately 2 to 4 cm in diameter, that develops about 7 to 30 days after inoculation of the fungus into the skin. Progressive induration leads to nodule formation with subsequent ulceration (Fig. 1). Further nodules appear in the lymph trajectory contiguous to the initial lesion (Figs. 2-4). The lesions tend to soften and may produce cutaneous fistulae. Systemic symptoms, if present, are usually mild. Regional lymphadenopathy is frequently found. The upper and lower limbs are the most commonly affected regions (Figs. 5-7). Bilateral disease is rare and

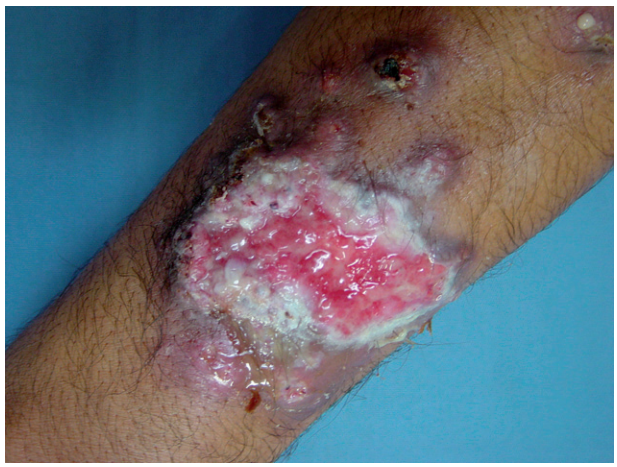

Fig. 4 Sporotrichosis of the left forearm showing ulceration and indurated nodules (same patient as in Figs. 2 and 3).

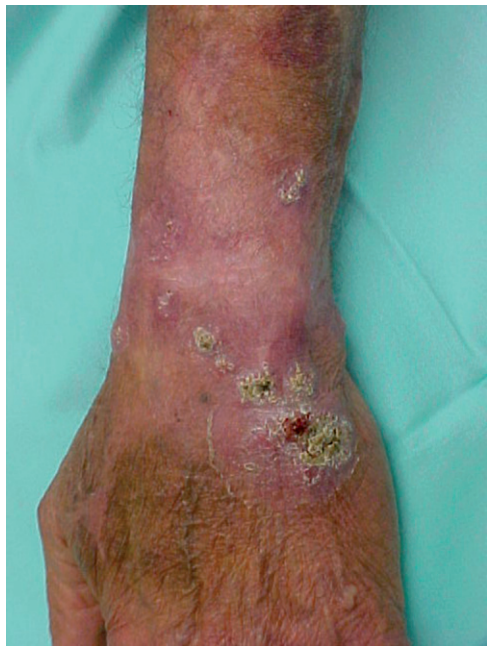

Fig. 5 Sporotrichosis of the left forearm showing ulceration and verrucous lesions.

would suggest multiple point inoculation related to the patient's professional activity.[22]

In some patients there is no lymphatic dissemination during the course of the disease, with the lesion remaining confined to the site of initial inoculation. This form is known as fixed cutaneous sporotrichosis. The lesions may be papular, plaque-like, nodular, verrucous, or ulcerated and can occur in the face, neck, trunk, or legs. Often they

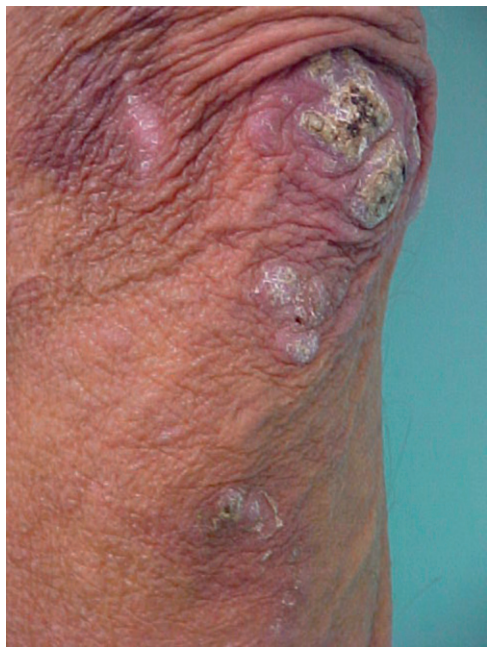

Fig. 6 Sporotrichosis of the left elbow with ulcers and verrucous lesions (same patient as in Fig. 5).

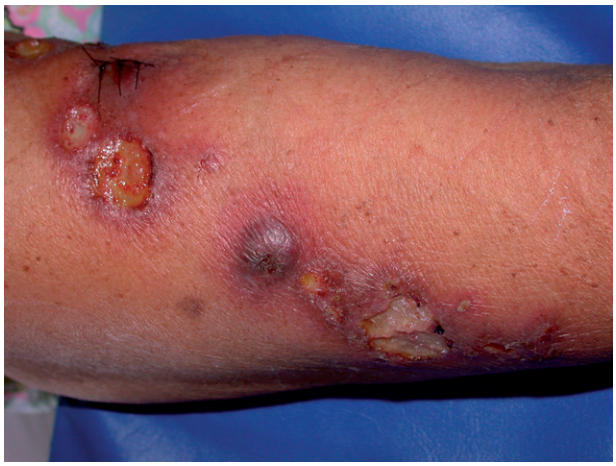

Fig. 7 Sporotrichosis of the right forearm in a patient with multiple myeloma.

become chronic because there is no tendency for spontaneous resolution.[13,21]

Both forms of cutaneous sporotrichosis may be accompanied by erythema nodosum during their evolution. Gutierrez-Galhardo et al[26] have postulated the hypersensitivity of the host exposed to the permanent domicile infection of infected cats as a possible mechanism for induction of erythema nodosum.

Disseminated or multifocal *S schenckii* infection is rare, and when it does occur, it is usually in the context of cellular immunodeficiency. It results from the hematogenic dissemination of the pathogen from the initial site of inoculation, whether cutaneous or respiratory. The disease can affect the skin, lungs, meninges, osteoarticular system, and boney skeleton. Some authors distinguish between disseminated systemic and disseminated cutaneous forms; however, such a distinction seems arbitrary because internal organ involvement occurs in most cases. Ten cases of disseminated cutaneous sporotrichosis without involvement of internal organs were reported by Salkup et al.[27]

Disseminated disease is almost always associated with an immunodeficient or debilitated state, whether from alcoholism, diabetes, sarcoidosis, tuberculosis, organ transplantation, malignancy, use of immunosuppressive agents, or AIDS. Until recently, only 3 cases of disseminated sporotrichosis were described in immunocompetent individuals.[27]

The clinical picture of disseminated sporotrichosis in end-stage AIDS is highly variable, producing phagedenic ulceration, acneiform lesions, hardened plaques, or crusts at presentation.[28] Death usually arises when there is pulmonary or meningeal involvement.

The extracutaneous form is even more rare and is difficult to diagnose because of the absence of skin lesions. It is caused by inhalation of spores or by hematogenic dissemination from a deep inoculation site. Osteoarticular infection is found in up to 80% of cases of extracutaneous disease.[17] Monoarthritis occurs with edema, synovial effusion, and limitation of normal function. The hands, wrists, elbows, ankles, and knees are the most frequently affected sites. Tenosynovitis, with or without carpal tunnel syndrome, is associated with deep inoculations. The diagnosis should be attempted through culture of synovial fluid or synovial biopsy because if untreated, the infection will lead to osteomyelitis.[29,30]

Pulmonary sporotrichosis typically affects men between 30 and 60 years with preexisting comorbidities. The clinical picture is similar to pulmonary tuberculosis with low-grade fever, chronic cough, and weight loss. Chest X ray shows unilateral or bilateral pulmonary fibrosis with cavitation. Hilar lymphadenopathy and pleural effusion may be present. Cytological analysis and induced sputum culture reveal the pathogen in most cases. Late-stage disease shows advanced fibrocavitatory pulmonary change with severe lung dysfunction.[30,31]

Sporotrichotic meningitis is an extremely rare event that is almost always associated with immunosuppression. In HIV-positive patients, disseminated or meningeal sporotrichosis occurs when the CD_4 T-cell count is less than 200 cells/mL.[30-32] Examination of the cerebrospinal fluid (CSF) reveals a lymphocytic pleocytosis with increased protein and hypoglycorrachia. Fungal culture of the CSF is required to establish a correct diagnosis.

Ocular sporotrichosis has been described and as for the remaining forms of extracutaneous disease, it can occur in healthy individuals.[33] Although few cases of genital sporotrichosis have been previously reported in the medical literature, a case of penile sporotrichosis is described by Kimyai-Asadi et al.[34]

Differential diagnosis

The differential diagnosis of cutaneous sporotrichosis includes leishmaniasis, paracoccidioidomycosis, chromoblastomycosis, blastomycosis, tuberculosis, bacterial pyoderma, subcutaneous abscesses of tularemia, primary syphilis, cat-scratch disease, and infections caused by atypical mycobacteria such as *Mycobacterium marinum*.

Differentiation of the fixed form of sporotrichosis from pyoderma gangrenosum can be very difficult. The case of penile sporotrichosis published by Kimyai-Asadi et al[34] had an initial diagnosis of pyoderma.

Laboratory diagnosis

For a definitive diagnosis of this mycosis, fungal culture should be performed. Pus, synovial fluid, sputum, blood, or tissue fragment is suitable for culture. Incubation is performed at 25°C using Sabouraud dextrose agar or potato dextrose agar. Colonies usually appear within 3 to 5 days and present a creamy white color that, in a few days, convert into the characteristic brown-black leathery colonies

(Figs. 8 and 9). In vitro fungal dimorphism with demonstration of conidia displaying a *bouquet* configuration on microscopy confirms the diagnosis.[30-32]

Some authors advocate direct examination using potassium hydroxide relying on the peculiar characteristics of the asteroid corpuscle for identification. Direct examination was shown to be diagnostic in 85.7% of cases, with confirmation by culture in 95.2%, in a study by Civila et al.[35] (Fig. 10)

The cutaneous sporotrichin test may be useful, except in cases of disseminated disease in which there is anergy.[30-32] There are no reliable serological tests for this disease.

Histopathology

Histopathological findings are generally nonspecific because the organism is not readily visualized in hematoxylin-eosin stain due to its polysaccharide coat; the fungal forms of the organism as well are not readily seen using standard periodic acid-Schiff (PAS) stain.

Sporotrichosis produces granulomatous inflammation associated with epithelial hyperplasia and a histiocytic plasma cell infiltrate. Asteroid corpuscles can be seen and constitute the fungal element surrounded by an eosinophilic material resulting from protein deposition that is responsible for the antigen and antibody reaction (Fig. 11).[30]

Although the pathogen may not be visualized at histopathology, Byrd et al[36] suggest that it would be possible to identify the fungus, even in individuals receiving immunomodulating medication, using routine microbiological staining method.

Treatment

Although cases of spontaneous resolution of sporotrichosis have been reported, most patients will require long-term treatment. Itraconazole (100–200 mg) is the treatment of choice in most cases, having an efficacy of ~100%.[37] For disseminated disease, amphotericin B is used in the initial treatment phase, with a switch to itraconazole for maintenance therapy. In endemic regions or in epidemic outbreaks, a saturated solution of potassium iodide (SSKI) remains an effective low-cost alternative.[38]

Potassium iodide

Historically, potassium iodide solution has been used as a treatment for sporotrichosis. It is a low-cost therapeutic agent, which is ideal for use in endemic regions in the developing world. The mechanism of action is unknown. Treatment is limited by side effects including gastrointestinal disturbance, coryza, rash, salivary gland enlargement, metallic taste, and thyroid dysfunction. Prolonged usage leads to the interruption of the endogenous production of thyroid hormones, a phenomenon known as the Wolf-Chaikoff effect.[13] The recommended dose in adults is 250 mg or 5 drops of SSKI (1 drop = 50 mg SSKI), increasing in increments of 3 drops (150 mg)/dose daily until a maximum dose of 30 to 40 drops (1.5–2.0 g) 3 times a day is achieved or until the patient experiences side effects. In children, the recommended dose is 3 drops 3 times a day, increasing by 1 drop per kilogram per dose to a maximum of 25 drops 3 times a day.[37] In the event of toxicity, the dose should be reduced to the level at which there are no intolerable side effects. Administration with fruit juices or milk may mitigate against gastrointestinal side effects. It is recommended that the therapeutic dose should be maintained for up to 4 weeks beyond the time of total clinical cure.[30,32]

Itraconazole

Itraconazole is the drug of choice in the treatment of localized cases, producing excellent cure rates, low relapse indices, and few side effects.[30] A case of conjunctival sporotrichosis that was successfully treated using 100 mg/d of itraconazole was reported.[33]

The effectiveness of itraconazole in the treatment of lymphocutaneous disease was demonstrated by Restrepo et al.[39] One hundred percent cure rates were achieved among 17 patients treated with itraconazole at a dose of 100 mg/d for 90 to 180 days (average 130 days) without any relapses during a follow-up period of 115 days.[39] A dose of 100 to 200 mg/d given for 3 to 6 months will achieve a cure rate of between 90% and 100%.[40] For children, the recommended dose of itraconazole is 5 mg/kg/d.

For osteoarticular sporotrichosis, Kauffman[41] recommend using 400 mg of itraconazole daily for 12 months. Using intra-articular amphotericin B with surgery, Bayer et al[42] achieved a cure rate of 83% for osteoarticular disease.

Amphotericin B

Amphotericin B is the drug of choice in the treatment of disseminated sporotrichosis or for patients with AIDS. The recommended dose is 0.5 to 1 mg/kg/d of amphotericin B, followed by itraconazole 400 mg/d as maintenance therapy, that is usually lifelong in HIV-positive patients.[34,40] Pulmonary disease can be treated with amphotericin B or itraconazole depending on the severity or the clinical picture. Central nervous system involvement should be treated with intravenous amphotericin B at 0.5 to 1 mg/kg/d, although higher doses of up to 2 mg/kg/d have been used. Such cases, however, are extremely rare with only 20 reported cases, including 4 HIV-positive patients.[37] A case of conjunctival sporotrichosis that was successfully treated using 100 mg/d of itraconazole was reported.[33]

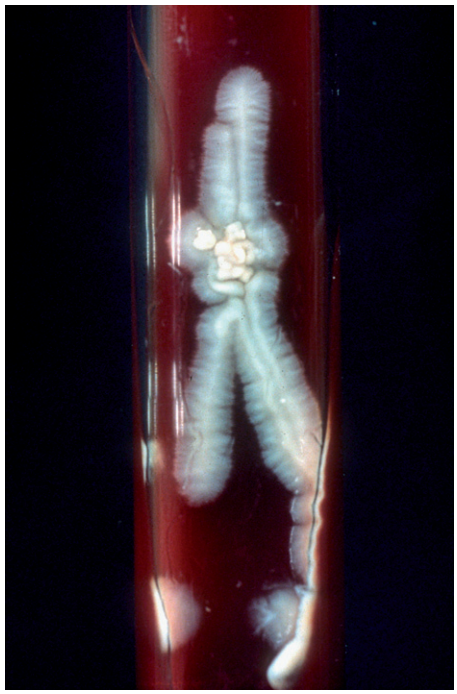

Fig. 8 *Sporothrix schenckii*—initial white culture growth (photo courtesy of Luiz Carlos Severo, MD, Porto Alegre, Brazil).

Heat therapy

The application of heat through heat compressors or infrared radiation is a nonpharmacological approach to therapy for limited cutaneous disease that may be more acceptable for pregnant mothers or for those intolerant of oral antifungal agents. For topical thermal compression, Bustamante and Campos[37] recommend application of thermal compressors at temperature of ~45°C to the affected site for 30 minutes, 3 times a day for at least 2 months. Overall, a 71% cure rate was observed in patients receiving thermotherapy by various methods.[43]

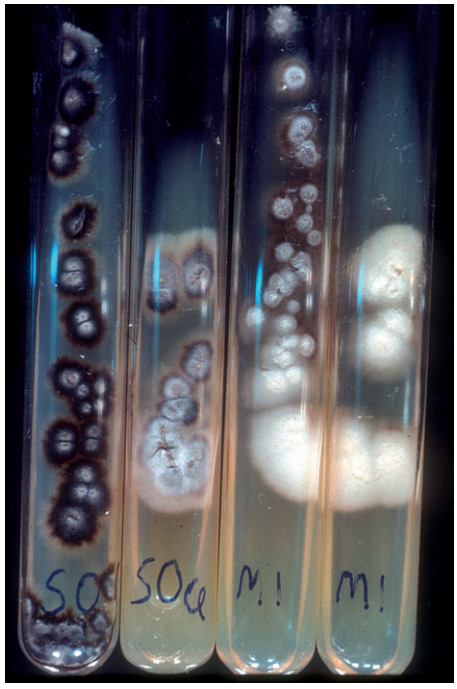

Fig. 9 *Sporothrix schenckii*—cultures darken as they mature (initial, white color; mature, black color) (photo courtesy of Luiz Carlos Severo, MD, Porto Alegre, Brazil).

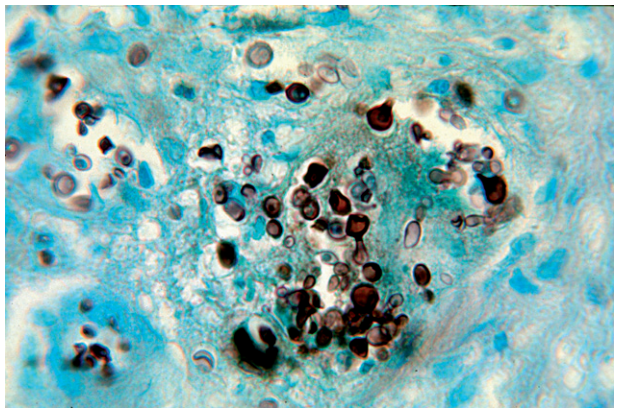

Fig. 10 *Sporothrix schenckii* direct examination from a patient with AIDS (photo courtesy of Luiz Carlos Severo, MD, Porto Alegre, Brazil).

New therapeutic approaches

The prospect of new therapeutical approaches lies in second-generation triazoles or the echinocandins that act by inhibition of 14 α-dimethylase enzyme through the cytochrome P450 system.[37] Morris-Jones et al[44] and Romero-Martinez et al[45] have identified melanin production as a putative virulence factor for *Sporothrix* and suggest that targeting melanogenesis might lead to new therapeutical agents.

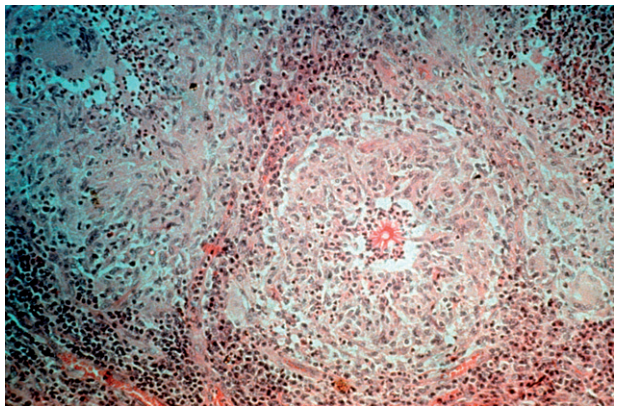

Fig. 11 Histopathology of *S schenckii*—asteroid corpuscle (hematoxylin-eosin stain, ×200 magnification) (photo courtesy of Luiz Carlos Severo, MD, Porto Alegre, Brazil).

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