Subcutaneous mycoses

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Subcutaneous mycoses include a heterogeneous group of fungal infections that develop at the site of transcutaneous trauma. Infection slowly evolves as the etiologic agent survives and adapts to the adverse host tissue environment. The main subcutaneous fungal infections include sporotrichosis, chromoblastomycosis, mycetoma, lobomycosis, rhinosporidiosis, subcutaneous zygomycosis, and subcutaneous phaeohyphomycosis. Diagnosis rests on clinical presentation, histopathology, and culture of the etiologic agents. This article considers sporotrichosis, chromoblastomycosis, and mycetoma.

**Epidemiology**

**Sporotrichosis**

\textit{Sporothrix schenckii} commonly occurs in nature as a saprophyte on dead plant material. Although this dimorphic mold is worldwide in distribution, it primarily grows in warm temperate and tropical climates. Its pathogenic potential was first reported by Schenck in 1898 \cite{1} at Johns Hopkins Hospital in Baltimore. When Schenck described it, he thought it resembled a “sporotricia.” Today, the fungus is known as \textit{S} \textit{schenckii}.

\textit{Sporothrix schenckii} most commonly gains entrance into the host through traumatic inoculation as a contaminant on thorns, splinters, barbs, grasses,
or sphagnum moss. The predominant clinical manifestation of the disease is lymphocutaneous sporotrichosis, which occurs chiefly in those whose occupation or vocation involves contact with vegetation and soil [2]. In addition, this form of the disease is generally associated with immunocompetent individuals 35 years’ of age or younger and in approximately equal numbers of males and females [3]. There is virtually no description of human to human transmission.

In contrast, disseminated sporotrichosis occurs in patients who are immunosuppressed. In the AIDS era epidemic, the numbers of such cases in HIV-infected patients is increasing [4–6].

Pulmonary sporotrichosis is found primarily in men, with a 6:1 male to female ratio. This form of the disease has been linked in one series of cases to alcohol abuse. Pulmonary sporotrichosis is probably caused by the inhalation of fungal conidia developing on vegetation, a situation similar to pulmonary infections caused by other dimorphic fungal pathogens [7].

Osteoarticular disease also has a male to female ratio of from 6:1 to as high as 9:1. Malignant disease and immunosuppressive therapy have been reported as predisposing factors. Most patients also have cutaneous and subcutaneous lesions, although some patients do not have histories of cutaneous disease.

The largest and most well-documented sporotrichosis epidemic occurred in South Africa between 1941 and 1944. Over 3000 gold miners acquired the lymphocutaneous form of the disease through contact with fungal-colonized mine timbers (Simson FW, unpublished data). The epidemic ended through treatment of the timbers with fungicides. Similar outbreaks have been described in the United States among individuals handling evergreen seedlings packed in sphagnum moss. The largest such epidemic occurred in 1988 and involved 84 forestry workers and home gardeners from 15 states [8,9]. The fungus seems to initiate infections only after the postharvest drying of the sphagnum moss for 4 to 24 months.

**Chromoblastomycosis**

Chromoblastomycosis refers to subcutaneous infections caused by darkly pigmented (dematiaceous) molds, which form thick-walled, dark-colored, multicelled structures called muriform cells or sclerotic bodies in tissue. As additional similar cutaneous and subcutaneous diseases were reported having only hyphal and yeast cells in tissue, these other infections were renamed phaeohyphomycosis [10,11].

Following the initial reports, a number of dematiaceous molds have been associated with subcutaneous lesions containing muriform cells. The most common of the etiologic agents are *Cladophialophora carrionii* and *Fonsecaea pedrosoi*. Less common pathogens include *Fonsecaea compactum*, *Phialophora verrucosa*, *Rhinocladiella aquaspersa*, *Exophiala jeansenmei*, *Exophiala spinifera*, and *Wangiella dermatitidis* [12]. To complicate matters further, as
illustrated in the following example, several of these molds may also cause other mycotic diseases and the diagnosis is not always straightforward.

A 38-year-old white man presented with a history of chronic lesions at the buttocks. He stated that the disease started 15 years ago, when he worked as a rural worker in the hinterlands of the State of Paraná, South Region of Brazil. During 2 years he was treated with two courses of amphotericin B (2 and 1.5 g) with partial response. He complained of pruritus and local pain. Erythematous, scaly, slightly elevated plaque, and cicatricial lesions on the buttocks were observed (Fig. 1). A skin biopsy showed muriform cells in the middle of microabscesses (Fig. 2). The cultivation of tissue fragments yielded black yeast, which was later identified as *E. jeanselmei* (Fig. 3 A, B). This patient has chromoblastomycosis. *Exophiala*, however, are classically causes of phaeohyphomycosis and mycetoma. When causing phaeohyphomycosis, pigmented yeast cells, vesicular structures, and septate hyphae are seen. In mycetoma, hyphae occur as compact dark aggregates.

Chromoblastomycosis is generally found in tropical and subtropical areas and in populations that do not routinely wear shoes. The etiologic agents gain entrance through puncture wounds, predominantly on the lower extremities. Dead plant contact is the major risk factor, although there may be some genetic susceptibility [13]. The primary pathogens include *F. pedrosoi* and *C. carrionii*. Both are common in tropical areas of the world, although *F. pedrosoi* is seen in humid forests, whereas *C. carrionii* is found in drier climates of Madagascar, Australia, China, Mexico, Cuba, and Africa. The largest series of chromoblastomycosis was collected in Madagascar by Esterre et al [31,70]. Over 40 years 1343 cases were identified, with 98% confirmed by the characteristic histopathology, and 69% by culture of *F. pedrosoi*. Its frequency is 1 per 920 inhabitants. In a separate hot and dry region of southern Madagascar, *C. carrionii* is the most common pathogen.

![Fig. 1. Violaceous plaque lesions and scarring on the buttocks.](image)
The risk of infection is higher here, because only 5% of the Madagascar population resides in this area, but more than a third of the total cases were from this region (1 per 480 inhabitants).

In a series of 325 cases from the humid Amazon region of Brazil, 77 of 78 culture-confirmed cases were caused by *F. pedrosoi* [14]. Most of the patients were male agriculture workers, and 81% developed lesions on the legs or feet. Londero and Ramos [15] found that most of their 35 patients in Rio Grande do Sul in Brazil resided in the northern part of the state, whereas there were few in the southern part, where people are engaged in cattle ranching and usually wear shoes. Occasionally, dissemination may occur to lymph nodes, the lung, and even the brain. The disease is commonly diagnosed after 1 to 4 years of slow evolution, but the lesions may slowly enlarge or persist for decades before diagnosis [16]. Spontaneous resolution is rare [17]. Queiroz-Telles et al [18] have reviewed 71 patients seen in the State of Paraná, in the South Region of Brazil chromoblastomycosis are characterized in Brazil, between 1985 and 1996. Table 1 summarizes these and other reports from Brazilian studies.

The disease was prevalent among males (12:1) with the mean age at the beginning of infection of 41.3 years (range 9 to 71 years). In 32 patients (45%), the infection was associated with trauma. Isolation of the etiologic agent was possible in 67 (94%) of the cases. *F. pedrosoi* was identified in 64 (95%) cases.
Mycetoma

Mycetoma is a syndrome involving cutaneous and subcutaneous tissues, fascia, and bone, caused by soil-inhabiting bacteria (actinomycotic mycetoma) or fungi (eumycetoma). Although the author who first described this disease remains in dispute, it was unquestionably originally found among Indian farmers [19] where it was called “Madura foot” or maduromycosis [20]. Mycetoma is the recognized general name of the disease whose clinical manifestations are described next [3,7].

Table 1
Chromoblastomycosis in Brazil

<table>
<thead>
<tr>
<th>State</th>
<th>No. of cases/years of observation (cases per year)</th>
<th>Sex M/F distributiona</th>
<th>Age</th>
<th>Duration in years</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rio Grande do Sul</td>
<td>73/28 (2,6)</td>
<td>7:1</td>
<td>40–50</td>
<td>1–40</td>
<td>[15]</td>
</tr>
<tr>
<td>Maranhao</td>
<td>13/03 (4,3)</td>
<td>5,5:1</td>
<td>50–60</td>
<td>0–15</td>
<td></td>
</tr>
<tr>
<td>Parana</td>
<td>71/11 (6,4)</td>
<td>12:1</td>
<td>40–50</td>
<td>1–50</td>
<td>[18,75]</td>
</tr>
<tr>
<td>PAara</td>
<td>325/55 (5,9)</td>
<td>13:1</td>
<td>50–60</td>
<td>?</td>
<td>[14]</td>
</tr>
</tbody>
</table>

a male:female.
Approximately 50% of all cases of mycetoma are caused by true fungi, the most common of which are *Madurella mycetomatis* and *Madurella grisea*. Less frequent etiologic agents of mycetomata include *Acremonium kiliense; E jeanselmei; Leptosphaeria senegalensis; Pseudallescheria boydii*, also known as *Scedosporium apiospermum*; and species in more than 10 other fungal genera [19]. The other 50% of infections called actinomycosis or actinomycotic mycetoma are caused by aerobic actinomycetes, primarily *Actinomadura madurae* and *Nocardia brasiliensis*.

As is the case for chromoblastomycosis, these fungi gain entrance to the host through penetrating trauma, abrasions, or contact with other sharp objects. Actinomycetoma and eumycetoma are most common in tropical and subtropical areas and are endemic to India and several countries in Africa and South America. For example, in a series of 21 patients observed in the State of Parana, Brazil, 14 (67%) were caused by bacteria (actinomycetoma) and 7 (33%) were caused by fungi. The mean age was 46.4 years (range 22 to 77), and lower limbs were involved in more than 90% of patients. Both forms of mycetoma have been reported from temperate climates, however, including the United States. The young to middle age male prevalence likely reflects more occupational contact [19].

**Pathogenesis**

**Sporotrichosis**

*Sporothrix schenckii* may gain entrance by either direct entry into tissue following traumatic injury, or by inhalation leading to pulmonary infection. *S schenckii* grows on dead, not living, plant material where it produces abundant hyphae and conidia. The hyphae and conidia serve as the inoculum that initiates cutaneous and lymphocutaneous sporotrichosis [21]. In contrast, conidia most likely initiate pulmonary sporotrichosis because of their small size and aerodynamic properties. Virulence of conidia is related to cell wall composition that is influenced by the age of the cells and the substrate the fungus was growing on [21]. The differential susceptibility seems to correlate with the amount of melanin present on the conidial wall. Melanin reduces phagocytosis and scavenging of oxygen and nitrogen species, which is protective for the fungus [22]. On entry into human tissue, the inoculum converts to a yeast form that elicits a local suppurative and granulomatous tissue response with nodule development spreading along the local lymphatic system. The use of local heat seems to be effective in the management of sporotrichosis because it increases the polymorphonuclear neutrophil leukocyte (PMN) killing ability [23]. Immediate and delayed-type hypersensitivity reactions are elicited by yeast surface alfa-L-rhamnopyranosyl units. Delayed-type hypersensitivity is one of the important host defense mechanisms that help prevent the spread of the fungus. The cell-mediated immune response against *S schenckii* is expressed mainly by
Macrophages activated by CD4+ T cells, resulting in a Th1 expression in the lesion [24,25].

**Chromoblastomycosis**

Chromoblastomycosis is essentially a miniature form of mycetoma. Chromoblastomycosis has muriform cells, whereas in mycetoma multicellular sclerotia are present. The structural architecture of muriform cells and sclerotia (granules composed of fungal cells) contribute to the recognition of the respective diseases (Fig. 4A). Muriform cells are expelled to the surface of the lesion by transepithelial elimination, whereas sclerotia are expelled through fistulae. Lesions consist of abscesses; have a granulomatous tissue response; and are noncontagious, chronic, and difficult to manage, especially in advanced infections. The etiologic agents of chromoblastomycosis are phylogenetically related fungi that are darkly pigmented in tissue because of the presence of melanin in their cell walls. Melanin may play an important role in the pathogenesis of infections caused by dematiaceous fungi. This pigment inhibits intracellular killing of *Wangiella dermatitidis* and blocks neutrophil oxidation [26]. Granulomatous and suppurative components of the patient’s tissue consist of lymphocytes, plasma cells, eosinophils, and Langerhans’ cells (see Fig. 4A). The fungus is either free, within phagocytic cells, or a combination of both [27]. In the dermis, muriform cells in microabscesses often show cell wall damage that may be the result of PMNs, in contrast to hyphal forms in the epidermis [28].

Rozental et al [29] have observed that once activated macrophages adhere to the cell wall of *F pedrosoi*, a respiratory burst occurs. The activity of the respiratory burst was detected in the macrophage plasma membrane portion that was in contact with the fungus, and within the phagocytic vacuoles. Even though the activated macrophages did not kill ingested fungal cells,
they delayed germination and hyphal development. Muriform cells of *F pedrosoi* may remain viable for up to 18 months after epidermal tissue is collected from the patient [30], demonstrating the resistant nature of these structures.

Specific antibodies to particular antigens of *C carrionii* (23.5 and 33 kd) and *F pedrosoi* (18.5 kd) correlate with the extent of lesions on the patient and the chronic nature of the infection. Some patients with chromoblastomycosis have had positive antibody for a year following antifungal therapy. A diagnosis of infection following a year of therapy can be detected using a quantitative ELISA test developed by Esterre et al [31].

**Mycetoma**

Fungi that cause eumycetoma are phylogenetically diverse. Sclerotia exhibit distinctive morphologic architecture, typically with cells having thickened cell walls toward the periphery of the sclerotium. Because of the irregular shape of sclerotia, the infection can be maintained in tissue by fragments of sclerotia breaking free from the parent structure and being dispersed locally either within the diseased area, or to adjacent tissue. PMNs are the predominant cell type in the inflammatory infiltrate that surrounds the sclerotia in tissue. Mycetomata are in essence granulomatous tumors [32].

**Laboratory diagnosis**

**Sporotrichosis**

The tissue phase consists of oval- to elongate-shaped budding yeast-like cells (Fig. 4B). Given the low numbers found in pus, exudates, or aspirates from lesions, however, fungal cells are rarely observed in potassium hydroxide or Gram-stained preparations. The use of celluflour or calcoflour-white, a nonspecific fluorescent stain, may enhance detection in clinical specimens.

Clinical diagnosis is dependent on culture using standard mycologic isolation media, (eg, Sabouraud’s glucose agar, Mycosel, blood agar) and incubated at 25°C to 30°C. *S schenckii* readily grows on these media within 5 to 7 days, although plates should be held 3 to 4 weeks. Colonies are initially moist and smooth, somewhat similar to those of yeasts, but become dry, wrinkled, folded, and tough in texture as they age. The black colony color is caused by the pigmentation in the conidial walls [3,7,33].

Because other molds are similar in their colony and microscopic morphology to *S schenckii*, it is important to demonstrate the dimorphic capabilities of the fungus. To do such, portions of hyphae and conidia from the mold phase are transferred to rich organic media, such as brain-heart infusion agar and incubated at 37°C to induce transformation to yeasts. Yeast colonies are dull white in color, smooth in texture, and composed of
spherical to oval budding cells, occasionally with multiple buds on a single yeast cell [3,7,33,34].

**Chromoblastomycosis**

Laboratory diagnosis is relatively easy because muriform cells are usually observable by direct microscopic examination of clinical specimens. Biopsy specimens show hyperkeratosis and parakeratosis, with central neutrophilic abscesses and granulomas. Tissue infiltrates may present with variable pigmented fungal structures, such as muriform cells (Medlar bodies, copper pennies, and fumagoid bodies). The muriform cells are the main diagnostic feature, and are defined as dematiaceous cells dividing in more than one plane (see Fig. 4A) [21]. They may be clustered with necrotic tissue as “black dots” seen on the surface of lesions.

**Mycetoma**

Exudate, pus, and biopsy tissue should be examined grossly for the presence of sclerotia (grains, granules), which are characteristic of both forms of mycetoma (Fig. 5). These are mounted on a microscope slide in potassium hydroxide and crushed under the coverslip. The sclerotia of actinomycetomata are composed of narrow filaments, generally less than 1 μm in diameter, along with coccoid elements. In contrast, the filaments that form the sclerotia of eumycetomata are from 2 to 6 μm in diameter. In addition, some of these hyphae may bear terminal swollen cells.

To isolate the etiologic agents of eumycetomata, sclerotia first should be transferred through several sterile water rinses containing antibacterial agents to decrease contamination that may inhibit fungal development. They can be inoculated directly into the mycologic media. To avoid contamination, tissue is best obtained from deep biopsy. Cultures should be incubated at 25°C and 37°C. Because the fungi that cause eumycetomata

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![Fig. 5. Mycetoma grain. H & E stain.](image)
are very slow growing, cultures are to be maintained for upward of 6 weeks before being discarded as negative.

**Clinical manifestations**

*Sporotrichosis*

Lesions are most commonly encountered as fixed cutaneous (Fig. 6) and lymphocutaneous (Fig. 7). The typical course of disease begins days to weeks after inoculation by the formation of a nodule or ulcer at the primary site of inoculation. Lesions enlarge slowly, and form satellite nodules tracking proximally along the regional lymphatics. Regional adenopathy may occur. The lesions of cutaneous sporotrichosis are characteristic but not pathognomonic. They may remit spontaneously, but often recur. *Nocardia* species can cause a very similar process (sporotrichoid nocardiosis [Fig. 8]) and rarely this can be seen with actinomycosis or with *Staphylococcus* infection [35,36]. Nocardiosis and actinomycosis can be identified readily by modified acid-fast stains of tissue biopsy specimens or abscess drainage. The differential diagnosis of nodular lesions with regional lymphatic involvement is broad enough to include certain nontuberculous mycobacteria, especially *M. marinum* and *M. fortuitum* complex, cat-scratch disease, and blastomycosis. The differential diagnosis of fixed and lymphocutaneous forms of sporotrichosis are as follows:

## Infectious diseases

### Fungi

- Paracoccidioidomycosis
- Blastomycosis
- Chromoblastomycosis
- Coccidioidomycosis
- Phaeohyphomycosis
- Granulomatous trichophytosis

### Bacteria

- Tuberculosis

Fig. 6. (A,B) Fixed sporotrichosis of the hand.
Syphilis
Nocardiosis
Ectima
Mycobacteriosis (*M. marinum* or *M. fortuitum*)
*Staphylococcus* lymphangitis
Protozoa
Leishmaniasis
Noninfectious diseases
Basal cellular carcinoma
Sarcoidosis

Lymphocutaneous disease may progress slowly over months. Bursitis may develop under the lesions, commonly in the olecranon or prepatellar sites [37–39]. Osteoarticular disease is less common, and may occur from direct extension from a cutaneous site, or may be blood borne. There may be no apparent primary focus for pulmonary or cutaneous disease [40]. Absence of sentinel skin lesions may lead to long delays in diagnosis. The series by Crout et al [40] had a mean of 25 months until diagnosis. Misdiagnosis may lead to intra-articular steroid injections, with temporary relief. Various surgical procedures may also be done before diagnosis [40].

Fig. 7. Lymphocutaneous sporotrichosis of the leg.

Fig. 8. Sporotrichoid nocardiosis.
Monoarthritic joint synovial swelling and effusion also are the usual manifestations, with the knee, ankle, wrist, and elbow being involved in descending order of frequency. Multiple joint involvement and widespread disease are usually seen in patients with underlying immune suppression. Fever is uncommon. Radiographs show bone erosions and osteoporosis [40,41]. Synovial fluid and tissue biopsy specimens are positive in culture. Organisms are seen far less commonly [40]. Nonarticular osteomyelitis may occur, usually under a site of local superficial trauma, and often without any overlying skin lesion [42].

Chronic pulmonary sporotrichosis is the least common manifestation of sporotrichosis; is most commonly a consequence of inhalation; and is marked by productive cough, dyspnea, and occasional hemoptysis (Fig. 9) [43]. Chronic cavitary disease and fibrosis are similar to chronic pulmonary forms of histoplasmosis, blastomycosis, coccidioidomycosis, or mycobacterial disease. Fibrocavitary disease is confined to the lungs and dissemination is uncommon. Underlying chronic pulmonary disease is common. Chronic pulmonary sporotrichosis is slow in onset and very slow in response. Residual fibrosis is common.

Disseminated sporotrichosis may spread from scratch inoculation at remote sites, from inhalation, or hematogenously (Fig. 10). Lynch et al [43] reported that none of their eight patients with arthritis had overlying skin lesion.
lesions. Widespread dissemination with meningitis occurs occasionally in immune-suppressed patients [44,45].

**Chromoblastomycosis**

Chromoblastomycosis and phaeohyphomycosis are chronic infections differing in clinical presentation and in parasitic morphology. Lesions, which develop at the site of inoculation and may occasionally spread by lymphatic and autoinoculation at remote sites, include the following:

- **Nodular type**
  Moderately elevated, fairly soft, dull to pink violaceous growths; smooth, verruciform, or scaly surface; with time they may become gradually tumorous.

- **Tumorous type**
  Tumor-like masses, prominent, papillomatous, sometimes lobulated; cauliflower-like; on the lower extremities tend to be more exuberant; the surface is partly or wholly covered with epidermal debris and crusts.

- **Verruciform type**
  Hyperkeratosis is the outstanding feature; frequently encountered along the border of the foot; dry lesion.

- **Cicatricial type**
  Nonelevated centrifugal growths that enlarge by peripheral extension at the center with atrophic or sclerotic scarring while healing takes place; tend to cover extensive areas of the body; usually present annular, arciform, or serpiginous contour.

- **Plaque type**
  Slightly elevated with variously sized and shaped areas of infiltration; generally found on the higher portions of the limbs; reddish to violaceous in color presenting a scaly surface; sometimes shows marked lines of cleavage.
Lesions may be graded both by type of lesion and by severity. The most severe lesions respond more slowly to treatment. The severity criteria of chromoblastomycosis lesions are as follows:

**Mild form**
A solitary plaque or nodule measuring less than 5 cm in diameter

**Moderate form**
Solitary or multiple lesions: nodular, verruciform, or plaque types, existing alone or in combination, covering one or two adjacent cutaneous regions, measuring less than 15 cm in diameter

**Severe form**
Any type of lesion alone or in combination, covering extensive cutaneous regions whether adjacent or nonadjacent

At the site of inoculation, lesions develop as warty papules or plaques (Fig. 11). They evolve over weeks to many months to thick, verrucous masses (Fig. 12). Older lesions may have central clearing, which reflects extensive scar formation or central ulcers (Fig. 13) [17]. Most lesions are solitary. The lesions of chromoblastomycosis can be grouped according to their severity or type, as shown previously [46]. This was useful in predicting the clinical response to itraconazole [18]. From the 71 patients, 17 (24%) presented mild forms; 32 (45%) moderate forms; and 22 (31%) severe forms. Their mean time of evolution was 9 (range 1 to 26) years; 15.7 (range 1 to 50) years; and 19.5 (range 5 to 40) years. A common misdiagnosis in very chronic lesions is cutaneous malignancy or premalignant conditions [17,47,48]. Comorbidities, such as leprosy or malignancy, can lead to poor therapeutic responses. Like sporotrichosis, the differential includes many infectious and noninfectious possibilities. The correct diagnosis is usually made with characteristic histopathology, and may be confirmed with cultures.

**Mycetoma**

Eumycetoma is distinguished clinically by an even slower course and greater destruction than chromoblastomycosis. Mycetoma remains the least common of these infections, although it has a wide distribution, pre-
dominantly in countries with hot climates and a protracted dry season [32]. Seventy percent of cases involve the foot. As with chromoblastomycosis, the illness is defined by the clinical presentation and pathology, not just by the organism isolated. The initial lesion may develop slowly or rapidly, with a painless papule or nodule followed by development of draining sinus tracts with visible grains (Fig. 14A). The sinus tracts rarely appear before 3 months, but are usually present by the end of the first year. Sclerotia may also be seen in pus discharging from the lesions (Fig. 14B). Sclerotia are a mix of fungal and host matrix components, and may include granuloma and fungal polysaccharide cytoskeleton products [49,50]. Although the lesions commonly do not spread beyond the initial focus, they gradually extend into deep tissues, extending along fascial planes to bone. Small pitted lesions develop in bones, and the cavities may become filled with sclerotia (Fig. 15). Secondary bacterial osteomyelitis may occur. The fungus may occasionally spread secondarily along lymphatics to involve viscera.

**Treatment**

*Sporotrichosis*

In a recent article, members of the Mycoses Study Group reviewed the data on treatment of sporotrichosis and put forth their recommendations [51]. Treatment options for sporotrichosis include hyperthermia, saturated
solution of potassium iodide (SSKI), ketoconazole, itraconazole, flucona-
zoole, the two newer triazoles posaconazole and voriconazole, and terbinafine
[2]. For lymphocutaneous disease, the least expensive treatment is SSKI,
increasing from 5 to 40 drops three times a day or the maximally tolerated
dose for 3 to 6 months (Table 2). SSKI is less effective or ineffective for
other forms of sporotrichosis. The other systemic drug used specifically for
skin infections is terbinafine. Initial reports were encouraging, with res-
ponses in five of five patients given 250 mg/d for 8 weeks [52]. In another
study, however, at 250 mg/d responses occurred in only about two of three
patients and it has not been aggressively pressed [53]. There are no data for
more severe forms of sporotrichosis.

Of the azoles, ketoconazole was the first explored. It is least well-tolerated
and least effective of the entire class, and the only thing favoring its use is the
low price. In one small study of seven patients, two responded, three failed,
and two relapsed [54]. In another similar study, Calhoun et al [55] found
that sustained remissions were noted in six of eight patients with systemic
disease, but late relapses occurred. Fluconazole is much better tolerated, but
even at doses of greater than 400 mg/d the response rate was only 71% for
lymphocutaneous and osteoarticular disease [56]. Neither of these drugs is
strongly recommended.
The most effective triazole by far is itraconazole, for both lymphocutaneous disease (responses 100% at 6 months’ treatment) [57] or for osteoarticular disease (about 85% to 100% response in several series [Table 3]) [57–60]. Pulmonary sporotrichosis is uncommon, and it may be difficult to evaluate improvement in people with extensively damaged lungs. Itraconazole may be useful, although experience is small. It is anticipated that both voriconazole and posaconazole, with potent extended spectra in other filamentous mycoses, will be highly effective; however, this is presently speculation with no supporting evidence.

For patients with the most acutely life-threatening disseminated disease, and those few with meningitis, amphotericin B has been recommended [2,43]. Patients with meningeal sporotrichosis are commonly immune suppressed, with such diseases as AIDS. Lifelong therapy may be required for these patients. Lifelong therapy with amphotericin B is a very unattractive proposition, and even in the absence of AIDS, there are reports of relapse [45]. Some recommend conversion to itraconazole when the patient is stable [2,51]. Although cerebrospinal fluid penetration of itraconazole is exceedingly low, itraconazole has been used successfully for treatment of both cryptococcal meningitis and coccidioidal meningitis. Pharmacokinetic arguments should not prevent clinical exploration. Except for lymphocutaneous disease, the length of treatment is not clearly defined. In the paucity of data, for osteoarticular disease and pulmonary disease the authors suggest

<table>
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<th>Table 2</th>
<th>Treatment options for sporotrichosis</th>
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<td>Form of disease</td>
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<tr>
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<td>Itraconazole</td>
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<tr>
<td>Bone and joint</td>
<td>Itraconazole</td>
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<tr>
<td>Pulmonary</td>
<td>Resection if possible</td>
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<td>Meningitis</td>
<td>Amphotericin B Unclear</td>
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Table 3
Itraconazole efficacy in sporotrichosis

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<tr>
<th>Reference</th>
<th>Lymphocutaneous</th>
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<tr>
<td>[59]</td>
<td>10/10</td>
<td>12/17</td>
</tr>
<tr>
<td>[60]</td>
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<td></td>
</tr>
<tr>
<td>[39]</td>
<td>0/3</td>
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<tr>
<td>Total</td>
<td>100% of 10</td>
<td>71% of 26</td>
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</table>

Responses/total number are given.
treatment of disseminated disease until the process is inactive, then for perhaps 6 additional months. This is obviously easier for triazoles than for amphotericin B, and the authors reserve amphotericin B for the most seriously ill. None of the triazoles are recommended in pregnancy, and either SSKI (skin disease), hyperthermia (awkward to perform), or amphotericin B are the major alternatives. Finally, some manifestations of sporotrichosis, particular bone and bursal disease, may warrant surgical resection or debridement [39,42].

Chromoblastomycosis

Patients with chromoblastomycosis are a true therapeutic challenge for clinicians. Before the availability of a broad range of antifungal agents, Yanase and Yamada [61] successfully treated a case of chromoblastomycosis caused by *F pedrosoi* by applying localized heat to the skin lesions with a pocket warmer. Subsequently, a number of patients in Japan who had disease caused by *F pedrosoi* were successfully treated with local heat, and in at least one instance with local heat and antifungal agents. Even though a number of patients had a complete cure, some had only local improvement. Local heat seems to be successful because *F pedrosoi* does not grow beyond approximately 37°C to 40°C, whereas local applied heat is approximately 46°C [62,63].

Cryosurgery has also been successful. Pimentel et al [64] treated 11 patients infected by *F pedrosoi*. The five cases having localized lesions were completely cured; three patients with generalized lesions attained clinical and mycologic remission for up to 26 months, whereas the three remaining patients with generalized lesions had significant improvement. Similar results have been reported by others [65]. Cryosurgery in conjunction with antifungal agents, such as itraconazole, has been successful [66,67].

The usefulness of local heat or cryosurgery is ideal for the management of small lesions (mild forms), whereas antifungal agents, such as itraconazole or terbinafine, are used for large lesions (moderate or severe forms). Fluconazole has been used successfully in a few patients [17,68]. Flucytosine has been used, with mixed results [69]. Unfortunately, even with systemic therapy, cure rates are not high. Bonifaz and Carrasco-Gerard [66] described their results for 51 cases from a 17-year period as 31% cured, 57% improved, and 12% failure based on cryosurgery, itraconazole, or a combination of both. Esterre et al [70] reported 47.2% cure with terbinafine in 43 patients.

Therapeutic success can be related to the etiologic agent (*C carrionii* is more sensitive than *F pedrosoi*); to the severity of the disease (edema and dermal fibrosis can reduce the antifungal tissue levels); and to the choice of the antifungal drug [18,71].

There are no comparative trials in chromoblastomycosis. In most of the clinical trials the lesions are not graded according to severity, nor did the different authors dealing with this mycosis use standardized criteria of cure.
Bayles [72] from South Africa introduced some years ago clinical, mycologic, and histopathologic criteria for the interruption of antifungal therapy in chromoblastomycosis patients. Queiroz-Telles et al [18] have been using these criteria and believe that they are very helpful for clinicians.

**Clinical**
- Disappearance of pain and itching and complete healing of all lesions with scarring

**Mycologic**
- Absence of parasites on direct examination
- No fungal isolation on culture
- Persistence of these findings in three consecutive monthly biopsy specimens

**Histologic**
- Absence of parasites
- Atrophy of the epidermis
- Disappearance of microabscesses and granuloma
- Replacement of granulomatous infiltrate by chronic inflammation and fibrosis
- Persistence of all these findings in three consecutive monthly biopsy specimens

Itraconazole alone or combined with fluconazole or topical liquid nitrogen (cryotherapy) seems to be the best treatment for chromoblastomycosis [73–76]. Borelli [71] published a small experience, the first with itraconazole. Restrepo et al [77] reported successes with itraconazole in chromoblastomycosis, with smaller lesions responding more rapidly than very large ones. Queiroz-Telles et al [18] reported 19 cases caused by *F pedrosoi*, with 42% cure with itraconazole. Those data have been expanded in number and follow-up to include now 30 patients (Tables 4, 5). The final assessment showed that eight patients (89%) with mild forms achieved clinical and mycologic cure after 10.9 months of therapy (range 7 to 17.6 months). No relapses were observed in this group after the mean time of 31.2 months (12 to 72 months). Similar responses were observed in 11 (91%) of the 12 patients with moderate forms after 12.9 months, on average (range 5 to 31 months of continuous treatment). In this group only one patient relapsed after 6.3 months of follow-up, and the remaining did not relapse in 12 to 60 months of follow-up. Among the nine patients with severe lesions of chromoblastomycosis, four (44%) had clinical and mycologic response after a mean of 30 months (range 10 to 51 months), and the remaining patients were significantly improved. One relapse was observed during the follow-up (after 35 months), but the patient improved again after resumption of therapy. No significant changes in the values of hematologic and biochemical tests were observed.
In another series of 12 patients, 11 with cultures positive for *F. pedrosoi*, lesions with areas less than 15 cm were treated with itraconazole, 300 mg/d [67]. Of four patients receiving just itraconazole, two were cured and two improved with courses of 8 to 14 months. Another group of four patients with similar-sized lesions received cryosurgery, with cures in all. In a third group, with larger lesions, itraconazole was used to reduce the size of lesions, which were then treated with liquid nitrogen. Others have used cryosurgery alone [65]. Two of four patients were cured, and two were improved. Other small case reports show success. A few cases have been treated with fluconazole, with some success, but experience is too small for a recommendation [68].

Flucytosine has been used successfully in a number of patients, often with amphotericin B or combined with itraconazole or resection [73,78]. It may be less well tolerated than the triazoles, however, and is not uniformly available in developing countries.

Terbinafine may be the best of all therapies. Esterre et al [70] have published a series of 43 patients from Madagascar, 37 with *F. pedrosoi* and the others with *C. carrionii*. Terbinafine was given at 500 mg/d for 6 to 12 months. Results showed efficacy in as short a time as 4 months in patients, half of whom had disease more than 10 years, and many of them azole failures. Sixty-five percent had achieved clinical cure by 1 year (Table 6). This has recently been tried in the United States, with one patient suc-

### Table 4
Clinical and demographic characteristics of 30 patients with chromoblastomycosis treated with itraconazole

<table>
<thead>
<tr>
<th>Clinical form</th>
<th>Number of patients (%)</th>
<th>Median age (years)</th>
<th>Duration of illness (years)</th>
<th>Previous treatmenta (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>9 (30)</td>
<td>57 (34–81)</td>
<td>7.5 (1–19)</td>
<td>4 (44)</td>
</tr>
<tr>
<td>Moderate</td>
<td>12 (40)</td>
<td>57 (42–70)</td>
<td>20 (6–50)</td>
<td>5 (42)</td>
</tr>
<tr>
<td>Severe</td>
<td>9 (30)</td>
<td>59 (50–75)</td>
<td>24 (18–40)</td>
<td>7 (78)</td>
</tr>
<tr>
<td>Total</td>
<td>30</td>
<td>56.5</td>
<td>17.2</td>
<td>16 (53)</td>
</tr>
</tbody>
</table>

a Surgery, cryotherapy, amphotericin B, flucytosine, and ketoconazole.

### Table 5
Efficacy of itraconazole in 30 patients with chromoblastomycosis

<table>
<thead>
<tr>
<th>Clinical and mycologic cure (%)</th>
<th>Duration of therapya</th>
<th>Improvement</th>
<th>Relapses posttherapeutic followupa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>8 (89)</td>
<td>10.9 (7–16.6)</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>11 (91)</td>
<td>12.9 (5–31)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>4 (44)</td>
<td>30 (10–51)</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

a median of months.
cessfully treated, and a similar experience in Japan with good efficacy in three of four patients reported [78,79]. Conclusions from these studies must be guarded, however, for several reasons. First, Esterre did not grade the severity of his patients, and he did not use histopathologic criteria for interruption of terbinafine. Second, the clinical specimens he used as mycologic criteria of response were just scrapings of the lesions. Finally, there are only preliminary findings and not long-term follow-up for relapse. In addition to cryosurgery with liquid nitrogen, hyperthermia has been used to treat chromoblastomycosis in very mild forms of disease [17,80]. Heat pads and even disposable pocket warmers have been used successfully [81].

Finally, the organisms seem sufficiently susceptible to amphotericin B that large oral doses might be used. Iijima et al [82] report one patient with *F pedrosoi* treated with up to 2400 mg/d (24 tablets) of amphotericin B. His small lesions cleared on this treatment. Amphotericin B concentrations in the bloodstream were only 0.089 μg/mL after a month of 300 mg/d, then 0.138 μg/mL after 2 weeks at 1200 mg/d. Clearly, this small amount of absorbed amphotericin B was sufficient to cure the patient. In the future, the new antifungal drugs under development may play an important role in the treatment of chromoblastomycosis. In vitro, dematiaceous fungi are very sensitive to the new triazoles voriconazole and posaconazole [83,84]. The results published to date suggest that these new agents have broad-spectrum activities in vitro; however, their effectiveness in the treatment of human mycoses remains to be determined.

**Mycetoma**

Eumycetoma is an extremely difficult infection to manage (Fig. 16). Because of its chronic course, surgical management does not have to be instigated before determining the identity of the etiologic agent. The agents of fungal mycetoma tend to respond differently to antifungal drugs [85]. This is a different situation than in chromoblastomycosis, where the etiologic agents are phylogenetically closely related to each other. Medical treatment is difficult because of the chronic nature of the disease, fibrosis...
and tissue damage, and the presence of the etiologic as sclerotia that serve as a protective structure for these fungi [32].

Management of fungal mycetoma is either medical, surgical, or a combination of both [32,86]. Depending on the severity and duration of the infection, the response to these modalities varies from complete cure to failure. Del Giudice [87] and Smith and Kutbi [88] recommend that several years may be required before a decision regarding final outcome is possible. When considering the chronic nature and slow progress of the disease, ample time must be allowed for the potential subsequent development of symptoms if the etiologic agent is still viable in the patient’s tissues. Surgery may result in mutilating excision to amputation with frequent recurrence involving regional lymph nodes and surrounding tissue because of inadequate adjacent tissue removal [44]. Small mycetomata are more successfully managed by surgery than are larger and more extensively developed ones [89]. Typically, antifungal agents are used in conjunction with surgical management.

Amphotericin B is thought ineffective, and fluconazole has produced only temporary improvement [56,86,90]. Ketoconazole has been thought to be the best drug for mycetoma, with 72% of Sudanese patients showing some improvement, but the data were generated before newer triazoles were available [91]. Itraconazole and terbinafine are presently the major antifungal agents considered for the medical management of fungal mycetoma.

Fig. 16. (A) Pretreatment eumycetoma. (B) Posttreatment same lesion. (C) Grains in a sinus tract
[44,88,92]. According to Poncio Mendes et al [93], itraconazole seems to be more effective than ketoconazole. In animal models of disseminated mycoses, the authors have found posaconazole highly effective against *P. boydii* (Gonzales G, Graybill JR, unpublished data), and there are some clinical responses documented to voriconazole [94]. It seems appropriate to develop these agents as alternatives, given the poor responses to date.

References


