

## Tropical dermatology: Fungal tropical diseases

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Fungal infections are common in tropical countries and can have an important impact on public health. Lobomycosis is a common fungal infection in the tropical rain forest of South America, and paracoccidioidomycosis (South American blastomycosis) is a widespread and sometimes severe illness. *Penicilliosis marneffei* is an opportunistic infection of AIDS patients in southeast Asia. Chromoblastomycosis and mycetomas are causes of morbidity around the world. Sporotrichosis is a worldwide subcutaneous mycosis with a high incidence in tropical countries and is an important illness in immunocompromised patients. Rhinosporidiosis was classed as a fungal infection but is now considered a protistan parasite that belongs to the class Mesomycetozoea. It is included in this review because of its historical classification. In the past, most of these mycoses were restricted to specific geographic areas and natural reservoirs. There are, however, situations in which people from other regions come in contact with the pathogen. A common situation involves an accidental contamination of a traveler or worker who has contact with a tropical mycosis. Even minor trauma to the skin surface or inhalation of the fungal conidia can infect the patient. Thus recognition of the clinical symptoms and the dermatologic findings of the diseases, as well as the geographic distribution of the pathogens, can be critical in diagnosis of the tropical mycoses. This review discusses some of the more common tropical subcutaneous and systemic mycoses, as well as their signs, symptoms, methods of diagnosis, and therapies. (J Am Acad Dermatol 2005;53:931-51.)

**Learning objective:** At the completion of this learning activity, participants should be able to recognize the clinical and histologic presentations of tropical fungal diseases with cutaneous manifestations and be familiar with the appropriate therapies.

**M**ycoses are responsible for major public health and economic problems. Nowhere is this relationship clearer than in tropical countries where these diseases are endemic or at least have a high incidence. The World Health Organization has acknowledged the importance of tropical mycoses and urged countries to recognize their impact, as well as to improve their mycologic awareness and capabilities.

Dermatologists from all over the world should be prepared to recognize and diagnose tropical myco-

### Abbreviations used:

CTL:	cytotoxic T lymphocyte
ELISA:	enzyme-linked immunosorbent assay
IL:	interleukin
PM:	paracoccidioidomycosis
TNF $\alpha$ :	tumor necrosis factor $\alpha$

ses. Many of them, such as sporotrichosis, commonly occur in the United States, and others can infect North American or European travelers to endemic areas. The mode of transmission can be a traumatic inoculation of the pathogen through the skin, such as in sporotrichosis, mycetomas, and chromoblastomycosis, or through inhalation of the fungus, as in paracoccidioidomycosis and penicilliosis marneffei. The incubation period can be as short as a few weeks for sporotrichosis or as long as years for lobomycosis. It is critical for the diagnostician to recognize the clinical pattern of lesions that can be restricted to the skin and mucous surfaces or even present as visceral dissemination.

Tropical mycoses can be subdivided into 3 major categories: superficial-cutaneous, subcutaneous, and systemic.<sup>1</sup> Superficial-cutaneous tropical mycoses include *Trichophyton schoenleinii*, which causes

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favus, found most often in the Middle East, South Africa, and South America. The most severe form of dermatophyte hair infection, favus presents as thick, yellow crusts composed of hyphae and skin debris (ie, scutula) and may result in scarring alopecia. Black piedra is a superficial phaeohyphomycosis caused by *Piedraia hortae* and is seen in Africa, Asia, and Central America. Tinea nigra is a superficial phaeohyphomycosis caused by *Phaeoannellomyces (Exophiala) werneckii* and is seen in the Caribbean, Asia, Africa, and Central and South America. Tinea imbricata presents as imbricate or concentric circular skin patches and is due to *Trichophyton concentricum*, which is found in the Pacific, Southeast Asia, and Central and South America.

Fungi with subcutaneous or systemic manifestations have the greatest medical importance and are the focus of this review. Mycoses with subcutaneous involvement include mycetomas, lobomycosis, chromoblastomycosis, and sporotrichosis. Geographically restricted mycoses with systemic dissemination are illustrated by paracoccidioidomycosis. Other systemic mycoses, such as histoplasmosis and cryptococcosis, are not restricted to tropical areas and affect patients all over the world. Coccidioidomycosis and blastomycosis are well known by American dermatologists and will not be discussed in this review.

## LOBOMYCOSIS

Lobomycosis, also known as keloidal blastomycosis or Lobo disease, is an uncommon and chronic subcutaneous mycosis that presents with numerous nodular lesions similar to keloids.<sup>2</sup> It is almost restricted to the geographic area of the Amazon rain forest in South America (Brazil, Ecuador, Bolivia, Colombia, Guyana, Peru, and Suriname).<sup>3-5</sup> Isolated cases have been reported in Mexico and in some countries of Central America (eg, Costa Rica and Panama)<sup>3,6</sup> and sporadically in France<sup>7</sup> and the United States.<sup>8</sup> Identification of the disease in dolphins (*Tursiops truncatus*), however, widened the known geographic distribution of the disease.<sup>9,10</sup> Two different subspecies of dolphins are frequently infected with the disease, and cases in Florida and on the Texas coast, the Spanish-French coast, and the Brazilian coast have been described.<sup>9,10</sup> Jorge Lobo first described this disease in 1931, but the source of the organism is still unknown.<sup>11</sup> Lobomycosis is the most common subcutaneous mycosis in Manaus, a Brazilian city of 1 million inhabitants on the borders of the Amazon river.<sup>4,6</sup> The incubation period is long, and a recent description of the case of an American citizen who traveled to Venezuela 2.5 years earlier and then developed a chest lesion of lobomycosis

suggests that this disease often goes through a long quiescent period that may range from several months to many years.<sup>8</sup>

A fungus similar to *Paracoccidioides brasiliensis*, the agent of South American blastomycosis, causes lobomycosis.<sup>3,12,13</sup> It has never been successfully cultivated.<sup>14,15</sup> Several names have been used to designate this pathogen, such as *Lacazia loboi*,<sup>15</sup> *Lobomyces loboi*, and *Paracoccidioides loboi*, but the name *Lacazia loboi* is the most commonly accepted.<sup>3,12,15</sup> Herr et al and Camargo et al performed a complete DNA sequence of the fungus and located it within the dimorphic Onygenales species and as a sister clade to *P brasiliensis*.<sup>14,16</sup> Its genome sequence is also similar to that of *Blastomyces dermatitidis* (North American blastomycosis) and *Histoplasma capsulatum*, suggesting that the agent is a dimorphic fungus with a mycelial stage in nature, as well as a yeastlike stage in the host.<sup>14</sup>

The organism has been transmitted successfully to an armadillo and to tortoises.<sup>17,18</sup> In addition, the infection has been maintained through 9 generations in the footpads of mice.<sup>19</sup> However, most of our knowledge of the etiologic agent of lobomycosis is derived from histopathologic and electron microscopic studies.<sup>15</sup> The fungus is abundant in lobomycotic skin lesions. It is a spherical intracellular yeast 6-12 nm in diameter.<sup>12,15</sup> The fungus is remarkably homogeneous, with an average diameter of 9 nm. *L loboi* is predominantly an intracellular pathogen.<sup>12</sup> Organisms, singly or in chains, reside predominantly in macrophage vacuoles. They probably reproduce by budding; linear or radiating chains of as many as 20 organisms linked by tubules have been observed.<sup>12,15</sup> The melanin-containing birefringent 1-nm-thick cell wall resists digestion by macrophages and may be central in contributing to the chronicity of the infection.<sup>8</sup>

The natural reservoir of *L loboi* is unknown. Its likely habitat is somewhere in the rural environment, because the disease occurs in human beings who live in rural areas.<sup>3,12-15</sup> Soil and vegetation seem to be likely sources of infection. The inability of *L loboi* to grow in culture and its unresponsiveness to most antifungal drugs suggests that it is an obligate parasite of some lower animal.<sup>14,15</sup> *L loboi* also has been recovered from lobomycotic lesions of *Tursiops truncatus* dolphins in Florida and in the Bay of Biscay in Europe; this finding implies that some aquatic reservoir also exists.<sup>9,10</sup> Lobomycosis presents similarly in humans and in dolphins; the skin lesions and morphologic features of the organism are nearly identical,<sup>20,21</sup> and at least 1 case of dolphin-to-human transmission has been documented.<sup>9</sup>

The disease affects mostly young male patients (21–40 years old).<sup>22</sup> Lobomycosis is uncommon but occurs in as many as 8.5% of the members of some tribes indigenous to South America, for example, the Amoruas tribe of the Casanare state in Colombia.<sup>23</sup> On the other hand, it is a rare disease among the Caiabi Indians (56 cases in the last 30 years) who live in the central highlands of Brazil.<sup>4,24</sup> The disease is usually found in tropical, humid, or subtropical forests with elevations greater than 200 meters, an average temperature of 24°C, and more than 200 cm of annual rainfall.<sup>3,4</sup>

The agent probably is introduced directly into the dermis through a penetrating injury, such as a thorn prick or an insect bite.<sup>12,13,25</sup> Although *L. loboi* and *P. brasiliensis* share a close genome sequence, there are significant differences between them.<sup>14,16</sup> While paracoccidioidomycosis is clearly a geophilic dimorphic fungus acquired through inhalation and dissemination from lungs to other organs, *L. loboi* is always localized in the cutaneous and subcutaneous tissues.<sup>12,26</sup> Moreover, because the disease also is found in dolphins<sup>9,10,20,21</sup> and most infected human beings live near aquatic environments, such as river borders, watercourses, intermittent creeks, and “igarapes” (from the Tupi Indian language, meaning “a natural narrow channel between a river island and the mainland”), it has been postulated that *L. loboi* is a hydrophilic fungus.<sup>3,4,21,22</sup>

Belone et al reported the use of BALB/c mice to maintain *L. loboi* for extended periods.<sup>27</sup> Considering the histopathologic findings, the clinical manifestations, and the finding of a higher number of fungi recovered than that inoculated into footpads of mice, the authors believe the BALB/c mice strain may be an excellent animal model to maintain and study *L. loboi* in the laboratory.<sup>27</sup> Moreover, even after serial passages of the fungi, the granulomatous lesions are reproduced consistently under laboratory conditions.

Skin lesions in infected persons develop slowly over time. For example, the incubation time in the patient who acquired the disease from an affected dolphin was 3 months,<sup>10</sup> and the incubation period in the American who had traveled to Venezuela was 2.5 years.<sup>8</sup> When a volunteer was inoculated with the etiologic agent, the lesion was 2 mm in diameter in the first month.<sup>28,29</sup> At 5 months the lesion was red papule 2 mm to 3 mm in diameter. At 15 months it measured 1 cm, with a small telangiectasis. At 25 months the lesion was 15 mm, and at 4 years it measured 33 mm in diameter and a 4-mm satellite lesion had developed.<sup>28,29</sup> Because of this slow growth, patients do not present themselves for treatment until many years have passed and usually after the lesions have become large.<sup>30</sup>

The lesions often begin as small papules or pustules and may occur at sites of minor trauma. The lesions may be mildly pruritic, or they may burn.<sup>29</sup> Occasionally a single lesion may regress and form a scar. However, the disease never disappears, and organisms are identifiable in the scar tissue.<sup>30</sup> Patients lack other systemic symptoms.

Patients commonly describe the very early stages of the disease as a “wartlike” lesion.<sup>22,26</sup> The typical keloidlike skin lesions appear only after several months<sup>31</sup> (Fig 1). The lesions increase in size by contiguity but also can spread from one site to another by autoinoculation.<sup>3</sup> Lesions have well-defined lobulated margins and are not attached to deeper structures.<sup>3,4</sup> The epidermis may be shiny, atrophic, and discolored. The disease may spread proximally from the extremities, suggesting lymphatic spread.

The most affected area is the pinna of the ear (50%), followed by the lower limbs (29%) and the upper limbs.<sup>3,22</sup> Differentiation of keloidiform lesions on the ears from lepromatous leprosy is difficult, but in lobomycosis the affection is unilateral.<sup>31,32</sup> Other important differential diagnoses are keloids, xanthomas, and dermatofibrosarcoma protuberans.<sup>3</sup> The typical appearance is “keloids over keloids.”<sup>3,5,6-9,32</sup> Ulcerations and gummatous lesions are not common,<sup>22,32</sup> but some verrucous lesions are often seen.<sup>22,24</sup> The increase in size and number of lesions is a slow process and can take several decades.<sup>24</sup> No deaths from lobomycosis have been reported.

It is not difficult to find the fungus in the tissue smear from the lesion. Direct microscopy can be performed with tissue samples obtained by means of curettage or surgical biopsy and macerated in 10% potassium hydroxide.<sup>12</sup> *Lacazia loboi* forms long chains of rounded and hyaline cells, each joined by a small tubule, with a thick and birefringent cell wall (Fig 2).<sup>13,14,30</sup> Sometimes there are more than 9 rounded fungal cells in a long chain.<sup>3</sup> It is not necessary to stain the smear because of the high number of rounded cells usually present in each sample,<sup>30</sup> but tissue sections can be stained with the use of periodic acid–Schiff digest, Grocott-Gomori methenamine-silver nitrate, or Gram stains.<sup>5</sup> The Grocott-Gomori methenamine-silver nitrate stain will allow the visualization of chains of darkly pigmented, spheroidal, yeastlike organisms.<sup>2</sup> Serologic tests have high sensitivity but lack specificity because of antigenic cross-reactivity with fungi from the genus *Paracoccidioides*.<sup>12,15</sup> The typical localization of the clinical lesions near extremities and the inability to grow in culture at 37°C suggest that *L. loboi* lost the capacity to grow at this



**Fig 1.** Lobomycosis. Keloidlike skin lesions over the upper limb. (Courtesy of D. Peryassu, MD.)

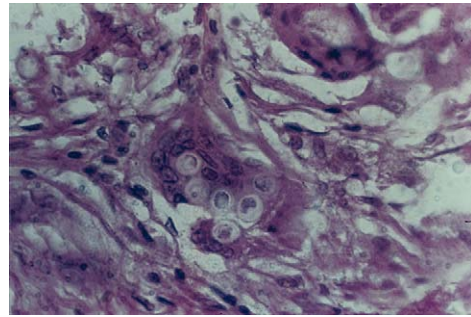
temperature, unlike other similar fungi.<sup>12,13</sup> This fact could explain the absence of visceral dissemination of lobomycosis and the preference for cooler areas of the body.<sup>3</sup> The cause for this characteristic could be adaptation to a hydrophilic life cycle.<sup>14</sup>

The most successful treatment is wide surgical excision of the affected area, since relapse is common.<sup>3</sup> Electrodessication is useful in early stages of the disease. Clofazimine at 300 mg/d has been used with good results in some patients.<sup>3,14,33</sup> The drug must be used, after initial clinical improvement, for at least 2 years at 100 mg/d. Antifungal drugs such as ketoconazole, itraconazole, amphotericin B, and 5-fluorocytosine are ineffective.<sup>3,22</sup>

## RHINOSPORIDIOSIS

Rhinosporidiosis is a chronic granulomatous infection caused by the hydrophilic agent *Rhinosporidium seeberi*. The disease is characterized by the chronic and benign evolution of polyps that primarily affect the mucous membranes, especially the nostrils and ocular conjunctiva; visceral dissemination is rare.<sup>34,35</sup>

The taxonomy of the agent has always been controversial. Guillermo Seeber, who first described the disease in 1896, considered the sporangium of *R seeberi* to be a sporozoan similar to coccidian.<sup>35</sup> The agent had been considered a fungus<sup>36,37</sup> but also



**Fig 2.** *Lacazia loboi*. Chains of rounded and hyaline cells with a double and birefringent membrane. (Hematoxylin-eosin stain; original magnification  $\times 250$ ; courtesy of D. Peryassu, MD.)

was interpreted as a protozoan parasite,<sup>38,39</sup> a cyanobacterium,<sup>40</sup> and a carbohydrate waste product.<sup>39</sup> Early researchers noticed the similarities between *R seeberi* and some aquatic parasites that lack a clear taxonomic classification.<sup>35</sup> Herr et al recently proposed that the organism should be considered in a new eukaryotic group of protists known as *Mesomycetozoa*.<sup>39</sup> Fredericks et al also agree with the concept of a novel clade of aquatic protistan parasites named *Ichthyosporea*, pointing to the similarities with other members of the DRIP clades (named for the organisms *Dermocystidium*, the Rosetta agent, *Ichthyophonus*, and *Psorospermium*) that infest fish and amphibia.<sup>38</sup> Ahluwalia suggested, however, that the causative agent of rhinosporidiosis is the cyanobacterium *Microcystis aeruginosa*, isolated from clinical samples as well as from water samples in which patients had been bathing.<sup>40,41</sup> It has been suggested that after gaining entry into the light-deprived environment in human epithelium, the photosynthetic cells of *Microcystis* differentiate into round bodies that characterize the histologic pattern of the disease.<sup>41,42</sup> No other human diseases are known to be caused by *Cyanobacterium* species.

The life cycle of the parasite is complicated. The mature forms of the organism, known as sporangia, contain multiple sporangiospores.<sup>41</sup> The trophocytes, the immature forms of *R seeberi*, are smaller and thinner than sporangia and do not contain endospores.<sup>37</sup> Sporangiospores are released at maturity and thereafter develop into trophocytes.<sup>34,37</sup> In arid countries most infections are ocular and dust is postulated to be a vector.<sup>43</sup> In most tropical areas, however, a close contact with rivers and lakes is associated with the disease and the most prevalent location is the nasal cavity.<sup>37,44-47</sup>

Immune responses to *Rhinosporidium seeberi* were studied both in mice and in human beings.<sup>48,49</sup>

The cell infiltration patterns in rhinosporidial tissues from 7 patients were evaluated with the use of immunohistochemistry.<sup>49</sup> The mixed-cell infiltrate consisted of many plasma cells, fewer CD68+ macrophages, a population of CD3+ T lymphocytes, and CD56/57+ natural killer lymphocytes, which were positive for CD3 as well. CD4+ T helper cells were scarce. CD8+ suppressor and cytotoxic-cytolytic cells were numerous. In lymphoproliferative response assays in vitro, lymphocytes from rhinosporidial patients showed stimulatory responses to mitogens. Lymphocytes from some patients, however, showed significantly diminished responses to rhinosporidial extracts in comparison with unstimulated cells or cells stimulated by mitogens, a finding that indicates suppressor immune responses in rhinosporidiosis.<sup>49</sup> The overall stimulatory responses with mitogens suggested that the rhinosporidial lymphocytes were not nonspecifically anergic.<sup>49</sup> The intensity of depression of the lymphoproliferative response in rhinosporidial patients bore no relation to the site, duration, or number of lesions or whether the disease was localized or disseminated. Rhinosporidial extracts showed stimulatory activity on normal control lymphocytes, perhaps indicating mitogenic activity.<sup>48</sup> These results indicated that enhanced immune responses develop in human rhinosporidiosis, while suppressed responses are also induced.<sup>49</sup>

Rhinosporidiosis occurs in the Americas, Europe, Africa, and Asia but is far more common in the tropics.<sup>34</sup> The greatest prevalence is in southern India and Sri Lanka, where the incidence is estimated at 1.4% of the pediatric population.<sup>50</sup> Some arid countries of the Middle East also show a high incidence of the disease.<sup>34,50</sup> South America is the second most common source of rhinosporidiosis, and the disease is endemic in the northeast part of Brazil, in a transitional environment between the Amazon rain forest and some arid areas where the rainfall is highly irregular, known as "caatinga."<sup>37</sup> The incidence of rhinosporidiosis in this particular Brazilian province is similar to the most affected areas of India, suggesting that both dry conditions and aquatic environments are related to the disease.<sup>37,50</sup>

The disease affects mostly males (70-90%), and the incidence is greater in those aged between 20 and 40 years.<sup>34,50</sup> Ocular infection is more prevalent in women, while nasal, and nasopharyngeal infections preferentially affect males.<sup>34,35</sup> The infection causes the development of painless intranasal papules that evolve into large and hyperplastic polyps studded with flecks (Fig 3). The surface of the polyp is irregular and red with some white dots, like small cysts, that correspond to the sporangia.<sup>37</sup> The nasal



**Fig 3.** Rhinosporidiosis. A polyp in the nasal passage. (Courtesy of I. Campbell, MD.)

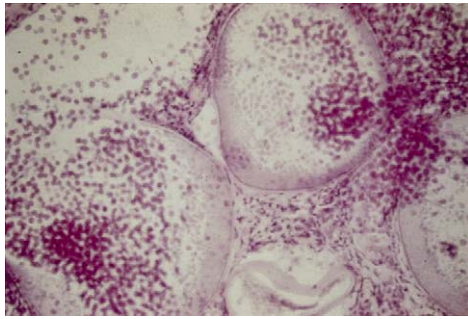
polyp is usually unilateral, pedunculated, and inside the nasal cavity.<sup>36,37</sup> The nodule is very friable, but exteriorization is not common.<sup>34</sup> Lesions may obstruct the nostrils and impair breathing, cause nasal bleeding,<sup>47</sup> or if the oral mucosa is involved, compromise speech and food intake.<sup>36,45-47</sup> Other mucosal sites involved less frequently include the palpebral conjunctiva,<sup>43</sup> oropharynx and nasopharynx, external ear canal, parotid duct cyst,<sup>51</sup> and genitalia. Visceral dissemination has been reported but is very uncommon.<sup>36</sup> The differential diagnoses must include pyogenic granuloma, coccidioidomycosis, and myospherulosis, an iatrogenic condition related to application of nasal substances.<sup>34,52</sup>

The diagnosis is based on the histopathologic demonstration of the characteristic thick-walled giant sporangia (Fig 4).<sup>34,53</sup> These structures range from 60 to 450  $\mu\text{m}$  or more in diameter and can contain up to 12,000 sporangiospores (7 to 15  $\mu\text{m}$  in diameter).<sup>37,53,54</sup> The organisms are abundant and appear in various sizes and stages of development. It is not necessary to perform special staining because of the size of the agent.<sup>37,54</sup> The cultivation of *R seeberi* was performed by Levy et al<sup>55</sup> but was not confirmed by other researchers.<sup>34,39,56</sup>

Treatment involves surgical removal of affected tissue, although recurrences are common. Local injection of amphotericin B may be used as an adjunct treatment to surgery to prevent reinfection and spread of the disease.<sup>36,37</sup>

### PARACOCIDIOMYCOSIS

Paracoccidioidomycosis (PM), also called South American blastomycosis or Lutz-Splendore-Almeida disease, is a chronic, progressive, and insidious systemic mycosis. It is fundamentally a pulmonary and lymph-nodal infection but may secondarily involve mucocutaneous sites.<sup>57,58</sup> The etiologic agent is *Paracoccidioides brasiliensis*, a thermally



**Fig 4.** *Rhinosporidium seeberi*. Thick-walled giant sporangia that contain numerous endospores. (Periodic acid–Schiff stain; original magnification:  $\times 100$ .) (Courtesy of I. Campbell, MD.)

dimorphic fungus. The disease is restricted to some countries of South and Central America, where it is the most widespread and serious systemic fungal infection.<sup>58,59</sup>

Adolpho Lutz first described the disease in a patient from Sao Paulo, Brazil,<sup>60</sup> and Almeida proposed the species name in 1930.<sup>61</sup>

PM occurs as far north as Mexico and in all of the South American countries, with the exception of Chile.<sup>58</sup> Brazil, in particular the southeast province, has the highest incidence, especially in forested tropical and subtropical areas.<sup>57,58,62</sup> Regions with acid types of soil, temperatures between 12°C and 30°C, altitudes between 150 meters and 2,000 meters, and pluviometric indices between 100 and 400 cm/y are the ecologic niches of the disease.<sup>63,64</sup> *P brasiliensis* was isolated from Amazonian armadillos and directly from the soil.<sup>63,65</sup> Bats and saguis, small monkeys from the southeastern forest of Brazil, are possible natural reservoirs.<sup>58</sup> Dogs, cattle, and horses also have antibodies against *P brasiliensis*.<sup>66</sup> It is possible that the normal habitat of the fungus is the soil or the plants that grow in these specific geographic regions, and both animals and men acquire the pathogen by aspiration.<sup>64</sup>

The mechanism that leads to the remarkable T-cell unresponsiveness to antigens in PM is still unknown. Campanelli et al investigated the involvement of cytokines, of Fas-Fas ligand–induced apoptosis, and of cytotoxic T-lymphocyte (CTL) antigen 4 engagement in the mediation of this phenomenon.<sup>67</sup> T-cell unresponsiveness was not associated with imbalanced cytokine production or with absence of CD28 expression, but patient T cells expressed higher levels of CTL antigen 4, annexin V(+), and Fas ligand. The addition of anti-Fas ligand decreased the levels of apoptosis, suggesting an activation-induced cell death triggered through the

Fas-Fas ligand pathway. Blockage of CTL antigen 4 and Fas ligand resulted in increased production of interferon- $\gamma$ . Moreover concomitant inhibition of Fas ligand and of CTL antigen 4 but not of transforming growth factor- $\beta$  resulted in significant T-cell proliferation in patients in response to phytohemagglutinin. Together these data showed that apoptosis mediated by Fas-Fas ligand and engagement of CTL antigen 4 are involved in modulation of the immune response in patients infected with *P brasiliensis*.

Pagliari and Sotto demonstrated epidermal Langerhans cells, CD34+ dermal dendrocytes, and cells expressing tumor necrosis factor  $\alpha$  (TNF $\alpha$ ), interferon- $\gamma$ , interleukin (IL)-5, and IL-10 in skin lesions of PM and quantified them by means of immunohistochemistry.<sup>68</sup> The findings of 61 biopsies were classified into 3 groups according to the pattern of tissue response: group 1, well-organized granuloma; group 2, poorly organized granuloma; and group 3, both kinds of granuloma. Langerhans cells had short and irregular dendrites in all groups and were decreased in number in groups 1 and 2. CD34+ dermal dendrocytes did not differ in number from the control group. Many cells expressing interferon- $\gamma$  characterized group 1. Groups 2 and 3 had large numbers of cells expressing IL-5 and IL-10. The data suggested that well-organized granulomas reflect a better cellular immune response, and the large number of cells expressing IL-5 and IL-10 in group 2 indicate an ineffective response in PM skin lesions. Both kinds of granuloma in the same cutaneous lesion probably represent an intermediate response between the anergic and hyperergic poles. Group 3 also showed higher numbers of cells expressing TNF $\alpha$  than did the control group. Some cells expressing TNF $\alpha$  were dendritic and localized around the granuloma, similar to the factor XIIIa+ dermal dendrocyte localization. According to Flavia Popi et al, *P brasiliensis* is able to synthesize an external glycoprotein (gp43) capable of inhibiting some dermal dendrocyte functions and evade cellular immunity.<sup>69</sup> Souto et al corroborated these findings in an experimental PM model in mice,<sup>70</sup> while Goldman et al analyzed the expressed *tag* sequence of the fungi in the yeast phase, with the identification of some putative genes related to virulence.<sup>71</sup>

Young and middle-aged men who work outdoors as farmers or hunters are at great risk for the chronic form of PM.<sup>58,72</sup> Adult women are rarely affected by this pattern of the disease, probably because of the suppressive effects of estrogens on mycelial-to-yeast transformation.<sup>73,74</sup> The acute form of the disease affects children and young adults of both sexes equally, however. The incubation period can



**Fig 5.** Paracoccidioidomycosis. Extensive stomatitis with a punctate vascular pattern.

reach several years, according to descriptions of travelers in whom the disease developed a long time after they visited endemic areas.<sup>58,75</sup>

The clinical manifestations of PM are polymorphous.<sup>57,58</sup> Inhalation of the fungi causes a primary lung infection characterized by productive cough, fever, and weight loss.<sup>58</sup> Direct inoculation of the parasite in both skin and oral mucous membranes is not common but can explain some cases of tegumental lesions without pulmonary involvement.<sup>76</sup> A common habit in Brazilian rural areas, the use of twigs to clean teeth, is the presumptive cause of these lesions.<sup>58</sup> The intestinal mucosa can also be the site of direct inoculation after the accidental ingestion of the fungus. The pulmonary route is, however, the most important one and is the site of inoculation in more than 96% of all patients with PM.<sup>58,59</sup> One-half of the patients develop subsequent oral lesions, often with nasal and pharyngeal ulcers.<sup>76</sup> These ulcerations are typical, having a punctate vascular pattern over a granulomatous base, and are known as Aguiar-Pupo stomatitis<sup>77</sup> (Fig 5). Dysphagia, hoarseness, and perioral crusted, granulomatous plaques also are common.<sup>58</sup> Gingival involvement may lead to tooth loss; in advanced cases the epiglottis and uvula also are destroyed, the hard palate is perforated, and the lips and tongue may become involved. These oral manifestations are followed by massive bilateral cervical lymph node swelling (Fig 6). Other lymphoid tissue sites, such as axillary, inguinal, and mesenteric lymph nodes, also can be affected.<sup>78</sup>

The cutaneous lesions of PM can vary from crusted papules to ulcers, nodules, plaques, and verrucous lesions. Centrifacial localization is typical of PM, and most of the lesions occur through dissemination of the oral and gingival lesions.<sup>58,59,76</sup> Most of the skin lesions, however, are the result of hematogenic dissemination of the fungus from the lungs.<sup>59</sup> The mucocutaneous involvement is marked



**Fig 6.** Paracoccidioidomycosis. Massive bilateral cervical and submandibular lymph node swelling and ulcerovegetative lesions on the face.

and may be due to the cooling effect of air in this region, which promotes growth of the fungus.<sup>76</sup>

The adrenal glands are affected in 48.2% of PM patients submitted to necropsy.<sup>6</sup> Lesions can affect long bones such as the ribs, humerus, and clavicle. Mesenteric lymph-nodal involvement may cause bowel obstruction and symptoms of an acute abdominal emergency.<sup>62,78</sup> Untreated PM also can be fatal owing to extensive pulmonary fibrosis, central nervous system dissemination,<sup>80,81</sup> or Addisonian syndrome.<sup>78,79,81</sup> Unapparent subclinical infection and minor lung changes are, however, common in affected areas and in Europeans and Americans who lived in these areas.<sup>58,62</sup> This primary benign disease is probably the most common presentation of PM.<sup>81</sup>

The differential diagnosis of PM is dependent on the clinical manifestations. Oral lesions can closely resemble mucocutaneous leishmaniasis. The lymph node enlargement is similar to sporotrichosis,<sup>58</sup> and the massive involvement of cervical lymph nodes is also seen with lymphomas, ganglionic tuberculosis, and actinomycosis.<sup>62</sup> Coexisting pulmonary tuberculosis is reported in almost 50% of patients with PM.<sup>59,81</sup> North American blastomycosis more commonly affects skin instead of mucosa and lacks regional lymphadenopathy; it often heals centrally



**Fig 7.** *Paracoccidioides brasiliensis*. Cultured at 37°C. Two views of a 15-day culture. (Courtesy of Hospital Central do Exército, Rio de Janeiro, Brazil.)

with atrophic scars, while cutaneous lesions do not resolve spontaneously in PM.<sup>62</sup>

Evaluation for PM is warranted in patients from endemic regions who have respiratory symptoms, oral or cutaneous lesions, and Addisonian syndrome.<sup>62,80</sup> The diagnosis is confirmed by means of culture or by finding characteristic multiple budding yeasts in tissue, material from lymph nodes, or sputum.<sup>82</sup> Yeast cells vary in size from 2 to 30  $\mu\text{m}$  in diameter, with narrow points of attachment of buds to mother cells.<sup>57,58,82</sup> The pattern of bud formation varies but often resembles a “Mickey Mouse head” or a pinwheel and helps in the differentiation from *Blastomyces dermatitidis*.<sup>62,82</sup> Fungus isolated from contaminated materials resembles popcorn if cultured at 37°C on Sabouraud dextrose agar medium for 21 days (Fig 7).<sup>58,59,82</sup>

The first immunologic reaction for PM diagnosis was developed by Fava-Neto and Raphael in 1955 using polysaccharide antigens of the fungus (Fava-Neto’s reaction).<sup>83</sup> Several other immunologic assays, particularly immunodiffusion, are valuable diagnostic adjuncts.<sup>84,85</sup> The intradermal reaction (paracoccidioidine) is not reliable for diagnosis in endemic areas.<sup>59,74,85</sup>

Slow-acting sulfonamides are the drugs of choice in the treatment of PM.<sup>58</sup> Both sulfamethoxypridazine and sulfadimethoxine, 0.5 g/d, following an initial dose of 1 g/d for 1 week are effective, but relapse is common.<sup>86</sup> Shikanai-Yasuda et al randomized 42 patients with active PM to receive itraconazole (50-100 mg daily), ketoconazole (200-400 mg daily), or sulfadiazine (100-50 mg/kg daily, up to 6 g daily) for 4-6 months, followed by slow release sulfa until the findings of serologic tests were negative.<sup>87</sup> All 14 patients in itraconazole and sulfadiazine groups and 13 in the ketoconazole group showed an adequate clinical response to the chemotherapy. One patient in the latter group showed treatment failure according to clinical and mycologic criteria.

The test of the hypothesis that the drugs reduced antibody levels with up to 10 months of treatment showed *P* values equal to 0.0001 for itraconazole, 0.017 for ketoconazole, and 0.0012 for sulfadiazine; this reduction was similar for the 3 groups. The authors were not able to show superiority of any one regimen over the others in the clinical and serologic responses of patients with the moderately severe form of the disease.<sup>87</sup>

Amphotericin B alone (3 mg/kg/d or on alternate days) or in combination with sulfamides is effective in severe cases of the disease.<sup>81,88</sup> Fluconazole is useful in patients with central nervous system lesions, and itraconazole is also useful in those with disseminated disease and progressive pulmonary infection.<sup>89</sup> Terbinafine has activity similar to that of itraconazole against *P brasiliensis* in vitro<sup>90</sup> and was used successfully to treat a case of disseminated PM (500 mg/d) with a follow-up of 2 years. Monitoring is performed with radiologic<sup>57,80</sup> and mycologic examinations,<sup>82</sup> specific enzyme-linked immunosorbent assay (ELISA),<sup>84</sup> and analysis of the improvement in the clinical lesions.<sup>58,59</sup>

## CHROMOBLASTOMYCOSIS

*Chromoblastomycosis*, also known as chromomycosis, Carrión mycosis, Lane-Pedroso mycosis, verrucous dermatitis, and black blastomycosis, is a term that designates a group of chronic cutaneous and subcutaneous mycoses caused by several species of dematiaceous (darkly pigmented) fungi.<sup>91-94</sup> Although common in rural areas, the disease lacks epidemic potential.<sup>92,95</sup>

First described by Pedroso and Gomes<sup>96</sup> in 1920, in Sao Paulo, as “a verrucous dermatitis of infectious origin,” the disease was named chromoblastomycosis by Moore and Almeida in 1935.<sup>97</sup> It is common worldwide but occurs mostly in tropical and subtropical areas of Africa, Asia, and South America.<sup>98-101</sup> The disease affects mostly laborers in rural areas, and the infection is much more common in men.<sup>100,101</sup> Going barefoot or wearing sandals enhances the susceptibility, because the fungi enter hands or feet after local trauma.<sup>101</sup> It is not a common disease in animals.

The disease is caused by a great number of fungi that inhabit the soil, plants, flowers, and wood. Five fungi usually are associated with chromoblastomycosis. *Fonsecaea pedrosoi* is the most common pathogen associated with the disease in tropical areas with a high pluviometric index.<sup>102-104</sup> *Phialophora verrucosa*, described by Medlar in 1915, is the second most prevalent fungus.<sup>105</sup> Carrion described *Fonsecaea compacta*, also known



as *Hormodendrum compactum*, in 1940, but it is not a common etiologic agent.<sup>106</sup> *Cladophialophora carrionii* (syn. *Cladosporium carrionii*) is the most important agent in dry countries and deserts in Australia, South Africa, and Cuba.<sup>95</sup> *Rhinocladiella aquaspersa*, described by Borelli<sup>107</sup> in 1972, is rare. Other rare fungi can cause the disease, such as *Wangiella dermatitidis*, *Exophiala spinifera*, and *Taeniolella boppii*,<sup>100,102</sup> which is now known as *Cladophialophora boppii*. Because these fungi reproduce in tissue by developing muriform septa rather than by budding, some have argued that the term “blasto” should be deleted from the name of the disease.<sup>99</sup>

The disease starts as skin-colored papules that enlarge and can ulcerate.<sup>92,95</sup> More often, however, the lesions will enlarge into nodules or plaques with a verrucous and scaly surface. These early lesions may resemble a dermatophyte infection with a dull red or violet color.<sup>91</sup> Sometimes the lesions can heal as sclerotic plaques, scars, or keloid formations.<sup>91,95</sup> In other cases, satellite lesions or peripheral expansion of the primary site may develop. The growth is always very slow and insidious.<sup>100</sup> After many years, some lesions evolve into the typical pattern of the disease: cauliflower-like masses, nodules, and sometimes, large vegetations<sup>92,95,101</sup> (Fig 8). Secondary lymphedema and pruritus are common characteristics, but the disease remains confined to the subcutaneous fat and does not invade underlying muscles and bone, except in immunosuppressed patients such as those who are using high doses of corticosteroids.<sup>95,108</sup>

The lower limbs are the most common site, but upper limbs, buttocks, ear pinna<sup>109</sup> (Fig 9), and nose also are affected by the infection.<sup>62-64,71</sup> Morbidity in chromoblastomycosis arises from secondary bacterial infection, disability of an affected body part, or transformation into a squamous cell carcinoma.<sup>91,92,95</sup>

The differential diagnosis of the verrucous lesions should include verrucous leishmaniasis, verrucous tuberculosis, sporotrichosis, and verrucous carcinoma.<sup>92</sup> Lobomycosis and paracoccidioidomycosis should be ruled out, as well as “mossy foot” and elephantiasis.<sup>92,95</sup> The diagnosis can be performed by detection of muriform cells referred to as sclerotic bodies (Fig 10) from tissue biopsies (dark-walled, polyhedral structures) or from fungal culture.<sup>108</sup> Sclerotic bodies are easily seen in potassium hydroxide preparations or with hematoxylin-eosin staining.<sup>102</sup> The muriform cells are often seen in the deeper portions of the lesion, whereas hyphae and budding cells may be present at the lesion surface. Owing to the transepidermal elimination process, chromoblastomycosis has been likened to a minia-



**Fig 8.** Chromoblastomycosis. Verrucous lesion.

ture mycetoma. Species identification is based on sporulation methods when the fungi are cultivated on media such as potato glucose or Lactrimel agar.<sup>102,108</sup>

The treatment of chromoblastomycosis is difficult. The response to oral antimycotic drugs is limited.<sup>100</sup> There are, however, some partial results with combination therapy with terbinafine (500 mg daily) plus itraconazole (50-100 mg daily)<sup>110</sup> or terbinafine alone.<sup>111</sup> Poirriez et al treated a severe case of chromomycosis with a combination of cryotherapy, shaving, oral 5-fluorocytosine, and oral amphotericin B (0.5 mg/kg/d).<sup>112</sup>

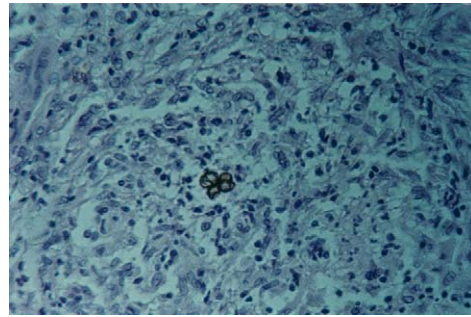
Surgical treatment is still the best choice to manage chromomycosis.<sup>91,92,95</sup> Surgery, electrodesiccation, and cryosurgery are effective in early stages.<sup>95,100-102</sup> Local heat can reduce substantially the extension of the lesions and the need for extensive surgeries. Successful therapy of *Fonsecaea pedrosoi* infection was observed through maintenance of the surface temperature at 46°C for at least 5 hours daily for 2 months and the use of a carbon dioxide laser.<sup>113</sup> Disabled or deformed limbs may require amputation.<sup>95</sup>

## MYCETOMA

Mycetomas are chronic infections of the skin and underlying tissues caused by both bacteria (actinomycetomas) and fungi (eumycetomas). They are



**Fig 9.** Ulcerative lesions on the ear pinna due to chromoblastomycosis. (Courtesy of Policlínica Geral do Rio de Janeiro, Rio de Janeiro, Brazil.)



**Fig 10.** Sclerotic bodies of chromoblastomycosis. (Hematoxylin-eosin stain; original magnification:  $\times 100$ ; courtesy of Policlínica Geral do Rio de Janeiro, Rio de Janeiro, Brazil.)

characterized by tumefaction of the affected area, multiple sinuses, and granules that contain the agent.<sup>114-117</sup> English physicians who worked in the Madura region of India during the 1840s provided the first descriptions.<sup>118</sup> The terms *maduramycosis* and *Madura foot* were derived from this first contact, but the disease is common in most tropical areas.<sup>118</sup> The term *mycetoma* denotes a fungal tumor, but bacteria cause most cases.<sup>119,120</sup>

Actinomycetomas are common worldwide, not just in tropical countries, but eumycetomas are especially common in equatorial Africa (Senegal, Somalia, Nigeria, and Sudan),<sup>121,122</sup> the Middle East,<sup>123</sup> India, and Mexico, where they are endemic.<sup>114</sup> Mycetomas occasionally are seen in the United States, particularly in the South.<sup>124</sup> They prevail in what is known as the mycetoma belt, which stretches between the latitudes of  $15^{\circ}$  and  $30^{\circ}$ , around the tropic of Cancer.<sup>114,124</sup> Actinomycetomas are the common type in South America,<sup>125</sup> and the true fungal mycetoma is not an endemic disease in the Amazon rain forest region. Male predominance is a constant finding in mycetoma, the sex ratio being 3.7:1.<sup>119-121</sup> This finding is commonly attributed to the greater risk of exposure to organisms in the soil during outdoor activities. No age is exempted, but the disease usually affects adults between 20 and 40 years of age.<sup>119</sup> Children and elderly people also may be affected in endemic regions.<sup>114</sup>

Mycetoma occurs most often in people who work in rural areas where they are exposed to acacia trees or cactus thorns that contain the etiologic agents that normally live as saprophytes.<sup>114,115</sup> Mycetoma is seen usually in farmers, hunter-gatherer populations, and field laborers.<sup>114,115,118,119</sup> However, the disease has also been found in persons who work in the city in various occupations, in victims of road accidents who have incurred a traumatic inoculation

of the agent,<sup>126</sup> and in travelers to tropical endemic areas.<sup>127</sup>

Several pathogens are associated with eumycetomas in different parts of the world, the main ones being *Acremonium* sp and *Madurella grisea* in Brazil,<sup>119</sup> *Madurella mycetomatis* in India and Africa,<sup>122,128</sup> and *Pseudallescheria boydii* in North America.<sup>114,129</sup> Actinomycetomas are caused either by endogenous anaerobic bacteria such as *Actinomyces israelii* and *Actinomyces bovis*<sup>130</sup> or by aerobic bacteria (*Actinomadura* sp, *Nocardia brasiliensis*, and *Streptomyces* sp).<sup>131</sup> Worldwide, approximately 60% of mycetomas are of actinomycotic origin.<sup>114</sup>

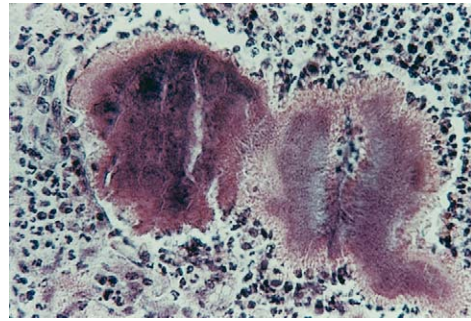
The organisms usually are present in the soil in the form of grains. The infecting agent is implanted into the host tissue through a breach in the skin produced by trauma caused by sharp objects such as thorn pricks, stones, or splinters.<sup>119</sup>

The clinical triad of swollen tissues, draining sinuses, and extrusion of grains characterizes the mycetomas.<sup>114,115,118,119</sup> They usually occur on the lower limbs, especially on the foot (79.2%),<sup>119,132</sup> but any exposed area is susceptible. The hand (Fig 11) ranks as the second most common site (6.6%), and other parts of the body that may be involved, though less frequently, include the knee, arm, head and neck, thigh, and perineum.<sup>133,134</sup>

Examination typically reveals painless tumefaction of the affected area. The skin is usually darker and firmer than that of the surrounding areas.<sup>133</sup> Early lesions are painless, indurated, subcutaneous swellings or papules at the site of previous trauma.<sup>129</sup> The swelling is usually firm and rounded but may be soft, lobulated, and often mobile; it grows slowly and tends to coalesce into larger lesions.<sup>133,134</sup> The rate of progress is more rapid with actinomycetoma than with eumycetoma.<sup>130</sup> In the former, the lesion is more inflammatory, more destructive, and invasive



**Fig 11.** Mycetoma on the hand.



**Fig 12.** *Nocardia brasiliensis* grains. (Periodic acid–Schiff stain; original magnification:  $\times 250$ ).

of the bone at an earlier period, whereas in eumycetoma, the lesion grows slowly with clearly defined margins and remains encapsulated for a long period.<sup>130,133,134</sup> Nodules, abscesses, and fistulae that drain a clear viscous or purulent exudate can be observed.<sup>118,133</sup> Granules of the microorganisms occasionally may be seen with the naked eye, as in the case of mycetoma caused by *Actinomadura madurae* and *Madurella mycetomatis*, among others.<sup>127,135</sup>

These initial lesions subsequently form multiple secondary nodules that may suppurate and drain through multiple sinus tracts with the extrusion of grains.<sup>133</sup> These sinuses may close transiently after discharge during the active phase of the disease or can also heal completely.<sup>114</sup> They are connected with each other, with deep sterile abscesses, and with the skin surface. Eumycetomas present more fibrosis, while suppurative and inflammatory patterns will predominate in actinomycetomas.<sup>114,130</sup> The subsequent invasion of the surrounding areas is a slow process that often destroys fascia and muscles.<sup>133</sup> Bone involvement leads to deformity and disability of the whole limb.<sup>136</sup> *Actinomadura* sp usually leads to massive bone destruction, while *Madurella* sp only causes a focal and restricted bone lesion.<sup>128</sup> HIV patients can present with destructive patterns of clinical lesions and pulmonary dissemination with chronic osteomyelitis and severe disability.<sup>137,138</sup>

Fahal et al suggested that mycetomas produce substances that have an anesthetic action, because even the larger lesions are usually painless.<sup>136</sup> At a late stage of the disease, however, the pain may become negligible owing to nerve damage by the fibrous tissue reaction, endarteritis obliterans, or poor vascularization of the nerve.<sup>114</sup> Pain may be produced by the expansion of the bone with the mycetoma granuloma and grains, or it may be due to secondary bacterial infection.<sup>136</sup> For unknown rea-

sons, the tendons and the nerves are spared until late in the disease process.<sup>114,136</sup> In the majority of patients, the regional lymph nodes are small and shotty. An enlarged regional lymph node is not uncommon and may be due to secondary bacterial infection, genuine lymphatic spread of mycetoma, or immune complex deposition as part of a local immune response to mycetoma infection.<sup>119</sup>

The differential diagnosis must include chronic osteomyelitis of other causes, botryomycosis, tuberculosis, Kaposi sarcoma, acral melanoma, and actinomycosis.<sup>118,119,134</sup>

Examination of the grains is critical to the diagnosis<sup>135</sup> (Table D). The grains can be examined grossly for color and texture and microscopically for hyphae or filaments, which will help in the differentiation between fungal or bacterial mycetoma.<sup>135</sup> White and yellow grains will prevail in *Pseudallescheria boydii* and *Acremonium* sp, while dark grains of brown or black will be more characteristic of an infection due to *Madurella mycetomatis*.<sup>135,139</sup> Grains can be cultured or crushed to be examined with Gram stain and potassium hydroxide preparations.<sup>119</sup> Eumycotic grains will reveal a mass of Gram-negative septate hyphae embedded in intercellular cement, and the filaments are wider than 1  $\mu\text{m}$ .<sup>134</sup> Actinomycotic grains have Gram-negative centers with Gram-positive, fine, radiating fringes that measure about 1  $\mu\text{m}$  in diameter<sup>135,140</sup> (Fig 12).

Culture of the lesion is performed through collection of the abscess or fistula secretion or by means of tissue biopsy.<sup>134</sup> In both cases the samples are cultured in media to isolate fungi (Sabouraud agar, mycobiotic agar) or bacteria (blood agar).<sup>114,134</sup> The etiologic agents are identified according to their macroscopic and microscopic features. Biochemical tests are particularly useful to identify actinomycetes.<sup>134</sup>

Serodiagnosis can help in the identification and classification of the various organisms and is helpful

**Table I.** Morphologic characteristics of grains associated with microorganisms causing mycetomas in humans

Agent	Color	Diameter (mm)	Consistency
<i>Actinomyces madurae</i>	White	1.5-2	Soft
<i>Actinomyces pelletieri</i>	Red	0.2-0.5	Hard
<i>Nocardia brasiliensis</i>	White or orange	<0.5	Soft
<i>Nocardia asteroides</i>	White	<0.5	Soft
<i>Streptomyces somaliensis</i>	Yellow	0.5-2	Hard
<i>Madurella mycetomatis</i>	Black	1-2	Hard
<i>Nocardiosis dassonvillei</i>	White or yellow	<0.5	Soft

for follow-up of patients.<sup>114</sup> The common serodiagnostic tests are immunodiffusion and ELISA, but cross-reactivity between some species is common. Several immunologic assays performed with the use of culture filtrate or cytoplasmic antigens of mycetoma agents have been developed to detect antibodies. In the case of *Nocardia brasiliensis*, it has been observed by means of Western blot that the humoral response is directed against 3 proteins of 24, 26, and 61 kd of a cellular extract.<sup>132</sup> These proteins were isolated and purified, and the 24- and 26-kd proteins were used to develop an ELISA test to detect antibodies against *N brasiliensis*. A correlation between antibody titers and clinical condition of the patients was observed. In those patients with active disease, the titers were high.<sup>132</sup> In patients with cured lesions, the optical density in the ELISA test was below the cutoff point, with results similar to those obtained with negative controls. To date, the use of a skin antigen for diagnosis has been of little help owing to the cross-reactivity with bacterial infections such as tuberculosis and leprosy.<sup>131,132</sup>

Immunodiffusion tests have been employed to detect antibodies in eumycotic mycetoma infections. In the case of mycetoma caused by *Madurella mycetomatis*, a humoral immune response has been observed in most of the patients against a cytoplasmic antigen of this organism.<sup>127</sup> A good animal model for the study of eumycotic mycetoma has not yet been developed.

Almost all mycetoma agents are osteophilic and cause a series of radiologic changes. In the early stages, there is a soft-tissue granuloma, which presents as a dense shadow or as scattered multiple soft-tissue shadows.<sup>128,136</sup> Calcification and obliteration of the fascial planes may be present. As the disease progresses, the bone cortex can be compressed by the granuloma to form multiple punched-out cavities through the normal density of the bone.<sup>136,140</sup> These cavities are the result of the replacement of the osseous tissue by the grains, and they are filled with solid masses of grains and fibrous tissue, which provides bone support.<sup>136,139</sup>

The ultrasonic appearance is considered to be characteristic in the diagnosis of mycetoma.<sup>135</sup> In eumycetoma lesions, the grains produce numerous sharp bright hyperreflective echoes and there are multiple thick-walled cavities without acoustic enhancement.<sup>86</sup> In actinomycetoma lesions the findings are similar, but the grains are less distinct because they are smaller and less consistent.<sup>135,141</sup>

Fine-needle aspiration cytology can be useful in mycetoma diagnosis.<sup>139</sup> The technique is simple, cheap, and rapid and can be tolerated by patients. Mycetoma lesions present an admixture of polymorphous inflammatory cells and grains. This technique can be used in routine diagnosis, in epidemiologic surveys of the disease, and for detection of early cases in which the radiologic and serologic techniques may not be helpful yet.<sup>140,142</sup>

Surgery is the most acceptable line of treatment for eumycetoma cases.<sup>114,143</sup> Usually it is in the form of aggressive surgical excision, debulking surgery, or amputation in advanced disease. Eumycetomas are well encapsulated, and great care must be exercised not to rupture the capsule, which may lead to contamination of the operative field by the fungal elements.<sup>143</sup> There are a few reports of clinical treatment in eumycetomas, some with ketoconazole and others with itraconazole.<sup>144</sup> The dose for both is 400 mg daily, but the treatment must continue for periods that range from few to many years. The liver function of the patients should be checked before and during treatment, as some of these drugs are hepatotoxic. The treatment usually is stopped with clinical, serologic, radiologic, and ultrasonic cure.<sup>118,134</sup> In all patients the medical therapy is started before surgery and continued postoperatively to avoid recurrence.<sup>145</sup>

The most important criterion for cure is the clinical resolution of the lesions, with the disappearance of the subcutaneous mass, healing of the sinuses, and return of the skin to normal.<sup>134</sup> Other important criteria include 3 consecutive negative findings of ELISA tests 1 month apart.<sup>115</sup> The bone

should regain its normal radiologic appearance with remodeling. No grains are seen in fine-needle aspiration,<sup>139</sup> and there is an absence of hyperreflective echoes and cavities at ultrasonic examination.<sup>141</sup>

Actinomycetomas are amenable to medical treatment with antibiotics and other chemotherapeutic agents. Combined drug therapy always is preferred over a single drug to avoid drug resistance and to eradicate residual infection.<sup>114,145,146</sup> The common drug regimen includes streptomycin sulfate (14 mg/kg/d) intramuscularly for 4 weeks; then it is given on alternative days along with diaminodiphenyl-sulfone (dapson) in the dose of 1.5 mg/kg twice daily.<sup>144</sup> If there is no response after a few months or if there are persistent side effects, then dapson is replaced by cotrimoxazole (14 mg/kg twice daily) or rifampicin (15-20 mg/kg/d). For massive lesions cotrimoxazole, rifampicin, and streptomycin sulfate can be combined.<sup>134</sup> The mean duration of the treatment is usually more than 1 year, but the cure rate varies from 60% to 90%.<sup>114,119</sup> Recurrence is more common after an incomplete course of medical treatment, and there is a good chance for the pathogen to develop drug resistance.<sup>134</sup> Treatment must be continued until the patient is cured. Medical treatment should be given pre- and postoperatively, as it facilitates surgery, accelerates healing, and reduces the chance of relapse.<sup>134</sup> Medical treatment is useful in all stages of actinomycetoma, even with advanced disease. Drug resistance and recurrence are commonly seen with incomplete and interrupted treatment.

Surgery is indicated in cases of actinomycetoma resistant to medical treatment or with bone involvement that does not respond to repeated long-term conservative treatment.<sup>143</sup> This type of mycetoma has an ill-defined border; therefore a margin of healthy tissue always should be excised with the lesion.

## SPOROTRICHOSIS

Sporotrichosis is a subcutaneous or systemic infection of human beings and animals caused by *Sporothrix schenckii*, a rapidly growing dimorphic fungus.<sup>147-149</sup> The organism derives its name from R. B. Schenck, who first reported the infection in 1898, according to Maslin et al.<sup>147</sup> *Sporothrix* typically exists as a saprophytic mold in soil, wood, or vegetative matter in humid climates worldwide.<sup>150,151</sup> A dimorphic fungus, the organism exhibits mycelial forms at 25°C and a yeast form at 37°C.<sup>150,152</sup>

The most common route of infection is the traumatic inoculation of the organism into the skin

through thorns or other plant matter.<sup>147</sup> Other, more unusual reported causes include squirrel bites and trauma induced by liposuction. Any compromise of the skin barrier with subsequent seeding potentially could cause infection. The agent then spreads by the lymphatic vessels to the draining lymph nodes and, in rare cases, to the underlying muscles and bones. Bloodstream dissemination is also rare.<sup>147,148</sup>

Sporotrichosis usually occurs sporadically as isolated cases. Occasionally groups of persons are infected after being exposed to the organism. An outbreak in the United States in 1988 affected 84 people who handled sphagnum moss.<sup>147</sup> An unusually large outbreak occurred in Africa in the 1940s in more than 3,000 miners who had frequent physical contact with wood timber supports.<sup>148</sup> Study of this outbreak contributed significantly to the current understanding of *S schenckii*, its growth patterns, and its mechanisms of dissemination. Finally, veterinarians, their assistants, and pet owners have been reported to be infected in small clusters, mainly by infected cats.<sup>153</sup>

The role of cell-wall compounds in the immune response to sporotrichosis is unknown. The effect of cell-wall compounds and exoantigen obtained from *S schenckii* in macrophage-fungus interactions was analyzed by Carlos et al with respect to nitric oxide and TNF $\alpha$ .<sup>154</sup> The lipid compound of the cell wall plays an important role in the pathogenesis of this mycosis and was found to inhibit the phagocytic process and to induce high liberation of nitric oxide and TNF $\alpha$  in macrophage cultures.<sup>154</sup>

The disease has a worldwide distribution but mainly is found in warm temperate and tropical zones.<sup>155</sup> Most reported cases occur in the Americas, Australia, Asia, and Africa. Sporotrichosis is rare in Europe.<sup>155,156</sup> The incidence of sporotrichosis in the United States is unknown.<sup>157</sup> As an unreported, sporadic disease, its incidence is difficult to estimate. The mold itself is endemic to the Missouri and Mississippi river valleys.<sup>157</sup> Sporotrichosis affects all ages and both sexes, but the majority of patients are younger than 30 years old and children under 10 are affected frequently.<sup>147,148</sup> The disease is related to occupation and therefore is seen more frequently in persons who come in contact with wood, plants, and soil, such as forest rangers, horticulturists, florists, carpenters, and miners.<sup>148</sup> Host factors like malnutrition, alcoholism, and impaired cell-mediated immunity may predispose to infection.<sup>158</sup>

Sporotrichosis infections can be either cutaneous or extracutaneous.<sup>147,148,156</sup> Cutaneous infections are most common and are subclassified into fixed

cutaneous and lymphocutaneous lesions.<sup>159</sup> Fixed cutaneous infections occur at the site of inoculation and remain confined entirely to the skin.<sup>159</sup> Lymphocutaneous disease results from lymphangitic spread of an infection. Satellite lesions develop along the path of the lymphatic vessels (sporotrichoid spread), and associated lymphadenopathy occurs.<sup>156</sup> Extracutaneous, or disseminated, sporotrichosis can present as pyelonephritis, orchitis, mastitis, synovitis, meningitis, or osseous infection.<sup>160</sup> Many affected persons have immunosuppression due to alcoholism or HIV infection, but pulmonary involvement is rare.<sup>147,158</sup>

Lymphocutaneous sporotrichosis is the most common presentation.<sup>159</sup> Symptoms usually arise within 3 weeks of injury. A subcutaneous nodule develops at the site of inoculation and may ulcerate as the result of central abscess formation.<sup>148</sup> The necrotic lesion opens through the skin to form an ulcer, called "sporotrichotic chancre," which is not painful.<sup>147,156</sup> Satellite lesions form along the associated lymphatic chain, and lymphadenopathy subsequently develops in a cordlike pattern.<sup>156</sup> The most common site is the upper limb and face.<sup>147,148,156</sup> The most important differential diagnosis should include lymphatic leishmaniasis, tuberculoid leprosy, and syphilis.<sup>156</sup> Untreated cases usually become chronic, but sometimes healing may occur.

Fixed cutaneous disease also is known as non-lymphatic sporotrichosis.<sup>159</sup> It appears as a scaly, acneiform, verrucous, or ulcerative nodule that remains localized. Satellite lesions and lymphadenopathy do not occur in this form of sporotrichosis.<sup>159</sup> It usually occurs as a reinfection in people who were previously sensitized to *S schenckii*. Spontaneous healing seldom occurs, and the differential diagnosis must include chromomycosis, leishmaniasis, and verrucous tuberculosis.<sup>156,159</sup>

Disseminated infection with *S schenckii* is unusual. Patients with AIDS appear to have an increased risk for dissemination if they develop sporotrichosis.<sup>158</sup> The diagnosis of lymphocutaneous sporotrichosis in a patient with AIDS should spark a search for dissemination to other sites, including the central nervous system.<sup>156,158</sup> The outcome for patients with AIDS is usually dismal, despite antifungal therapy, although a few cases of sustained remission, if not cure, have been reported.<sup>158</sup> Disseminated disease can result in pyelonephritis, orchitis, mastitis, arthritis, synovitis, meningitis, osseous infection, or, rarely, pulmonary disease.<sup>150</sup> Most cases of primary pulmonary sporotrichosis are due to inhalation of the spores that can cause diffuse fibrosis or abscesslike cavities with

enlargement of the mediastinal lymph nodes.<sup>147</sup> Cutaneous lesions can occur in the setting of disseminated infection and start as erythema nodosum,<sup>161</sup> which become papules, pustules, ulcers, and gummata.<sup>156</sup>

*S schenckii* readily grows on Sabouraud dextrose agar or brain-heart infusion agar at 25°C as a lobate, smooth or verrucous, moist, cream-colored colony with occasional aerial mycelium, maturing to a black leathery colony.<sup>156,162</sup> Yeast growth at 37°C must be demonstrated to confirm *Sporothrix*.<sup>163</sup> The organisms are characteristically scarce in tissue and may not be detected with tissue stains alone; therefore cultures are essential.<sup>162</sup> Polymerase chain reaction is also effective in the diagnosis of sporotrichosis, even in fixed cutaneous lesions with few parasites.<sup>164</sup>

Sporotrichosis is usually difficult to diagnose by means of histopathology.<sup>147</sup> A nonspecific granulomatous reaction with pseudoepitheliomatous hyperplasia is typically present.<sup>148</sup> Rarely, periodic acid–Schiff staining reveals the round to oval, cigar-shaped spores within the granuloma. The rare extracellular asteroid bodies of eosinophilic spicules that surround a central yeast are specific for sporotrichosis, as asteroid bodies seen in other granulomatous reactions are intracellular, filamentous myelin figures that contain lipid.<sup>147,148</sup>

Several systemic antifungals and sometimes local hyperthermia are beneficial as treatment of fixed cutaneous sporotrichosis.<sup>165</sup> This therapy entails weeks of daily applications to the lesions and requires that the patient faithfully apply heat that will warm the tissue to approximately 42°C.<sup>156</sup>

Itraconazole has become the drug of choice for treatment of lymphocutaneous sporotrichosis and for fixed lesions, with an expected success rate of 90%–100% based on open treatment trials of 100–200 mg daily.<sup>165–167</sup> Children with sporotrichosis can undergo safe treatment with itraconazole. Dosages of either 100 mg daily or 5 mg/kg daily have been used for the small number of children who have undergone treatment with itraconazole.<sup>165</sup> Fluconazole is second-line treatment for sporotrichosis.<sup>165</sup> It is less effective than itraconazole and should be used at a dose of 400 mg only if the patient cannot tolerate itraconazole. Ketoconazole is less effective than fluconazole and should not be used to treat sporotrichosis.<sup>165</sup>

Saturated solution of potassium iodide has been used since the early 1900s.<sup>168</sup> Although the mechanism of action is unknown, this agent was the standard treatment for lymphocutaneous sporotrichosis up until the last few years.<sup>168,169</sup> It is inconvenient to take, and side effects, including metallic

taste, salivary gland enlargement, and rash, are common. However, because saturated solution of potassium iodide is much less costly than other agents, it still is recommended. Treatment usually is initiated with 5 drops 3 times daily and is increased as tolerated to 40-50 drops 3 times daily. Saturated solution of potassium also has been used as treatment for children at dosages of 50 mg or 1 drop 3 times daily, up to a maximum of 500 mg or 10 drops 3 times daily.

Terbinafine has been used as treatment for a few patients and appears effective. However, too few data are available to recommend its use until ongoing clinical trials are completed.<sup>165</sup> Although effective, treatment with amphotericin B is not recommended because of toxicity and inconvenience of administration and because lymphocutaneous sporotrichosis is commonly a localized and non-life-threatening infection. Amphotericin B is indicated, however, for patients with life-threatening or extensive pulmonary sporotrichosis.<sup>165</sup> The most effective therapy appears to be a combination of amphotericin B and subsequent surgical resection. However, many patients are unable to tolerate such a procedure because of severe underlying pulmonary disease. Itraconazole at a dosage of 200 mg twice daily can be used as initial therapy for patients who have non-life-threatening pulmonary sporotrichosis.<sup>165,166</sup> On the basis of anecdotal case reports, amphotericin B is the drug of choice for treatment of disseminated infection with *Schenckii*. Itraconazole may prove beneficial for lifelong maintenance therapy for patients with AIDS after a course of amphotericin B and can be tried as initial therapy for non-life-threatening disease in those patients in whom amphotericin B cannot be tolerated.<sup>170</sup> No data support the use of other drugs for the treatment of disseminated sporotrichosis.

Pregnant women with sporotrichosis should not receive azole therapy because of the teratogenic potential of this class of drugs, nor can they undergo treatment with saturated solution of potassium iodide because of its toxicity for the fetal thyroid.<sup>168</sup> Terbinafine has not been approved for use in pregnancy. Amphotericin B is relatively safe during pregnancy but should be used only for treating disseminated or pulmonary sporotrichosis.<sup>165</sup> One option for cutaneous disease is local hyperthermia; another option is to wait until the pregnancy is completed and then initiate itraconazole therapy.<sup>165</sup> There is no risk of the infection disseminating to the fetus, nor is sporotrichosis worsened with pregnancy; thus little risk is involved with delaying treatment of cutaneous or lymphocutaneous sporotrichosis.



**Fig 13.** Umbilicated papules of *Penicillium marneffeii* on the face of an AIDS patient from Myanmar.

### PENICILLIOSIS MARNEFFEII

In some southeast Asian countries, the thermally regulated dimorphic mold *Penicillium marneffeii* has recently increased in importance to the point that it is an indicator organism of advanced cases of HIV disease. Cases have been reported in patients living in Manipur State, India, Myanmar, Malaysia, portions of southern China, Hong Kong, and Taiwan. The majority of cases occur in northern Thailand<sup>171</sup> where *P marneffeii* is more common than cryptococcosis. Infection caused by *P marneffeii* is an AIDS-defining illness as defined by the Thai Department of Communicable Disease Control.<sup>172</sup>

*P marneffeii* is a thermally regulated dimorphic fungus that grows as a typical species of *Penicillium* at room temperature and as yeast cells that divide centrally by fission within phagocytic cells. Owing to its intracellular nature and oval shape, some cases of penicilliosis marneffeii have been histologically confused with histoplasmosis. *P marneffeii* is readily distinguished in tissue from *Histoplasma capsulatum* by having yeast cells that divide by fission. A diffusible red pigment that is produced in culture is one of the first indications that an isolate may be *P marneffeii*. Even though the fungus has been isolated from bamboo rats, its natural habitat is most likely decaying vegetative material or soil. Bamboo rats are simply another host for this opportunistic human pathogen.

Prior to the AIDS pandemic in southeast Asia, infections caused by *P marneffeii* were exceptionally rare. The increased number of immunocompromised individuals has provided a large risk population for infection. In Hong Kong alone, about 10% of AIDS patients have penicilliosis marneffeii infection, whereas 25% of AIDS patients attending J. N. Medical Center, in Imphal, Manipur state, had disseminated penicilliosis.<sup>173,174</sup>

In addition to individuals with HIV, penicilliosis marneffeii has occurred in patients having Hodgkin's

disease, tuberculosis, systemic lupus erythematosus, and autoimmune disease. Periodically, cases are described in patients who are living in areas outside the endemic zone. These individuals typically have a history of travel to an endemic area.

Initiation of penicilliosis marneffeii presumptively begins by the inhalation of *P marneffeii* conidia. Pulmonary alveolar macrophages are the primary host defense mechanism. *P marneffeii* is a pathogen of the reticuloendothelial system where it can be found as a proliferating yeast within phagocytic cells. In patients with normal immunity, the host response is granulomatous or suppurative. Immunocompromised individuals have a necrotizing reaction.<sup>175</sup> In AIDS, the infection develops late in the course of the disease when the CD4+ cell count is less than 50 cells/ml. Clinical presentation includes fever, anemia, weight loss, lymphadenopathy, hepatomegaly, and characteristic papules with central necrotic umbilication that occurs in approximately 75% of patients.<sup>173,176</sup> Owing to hematogenous dissemination, the yeast form of the pathogen can often be detected in blood and bone marrow specimens.<sup>177</sup>

The majority of cutaneous lesions are umbilicated papules with or without central necrosis that are similar to molluscum contagiosum (Fig 13). The lesions are distributed primarily on the upper half of the body. Interestingly, umbilicated papules are common on the oral mucosa.<sup>173</sup> In addition to molluscum contagiosum, the differential diagnosis includes histoplasmosis, cryptococcosis, and some viral infections. The fungus can be readily isolated from skin lesions and a PCR-based method for skin diagnosis has been developed.<sup>178</sup>

Isolates of *P marneffeii* are sensitive to itraconazole.<sup>179</sup> Treatment with amphotericin B (0.6 mg/kg/day) for 2 weeks followed with oral itraconazole (400 mg/day) for 10 weeks is effective. Unfortunately, relapse is common approximately 6 months after discontinuation of this therapy. Lifelong suppressive itraconazole therapy is now recommended for AIDS patients.<sup>175</sup> In a recent study, relapse did not occur in patients being treated with itraconazole secondary prophylaxis.

## OTHER SUBCUTANEOUS AND SYSTEMIC TROPICAL MYCOSES

Phaeohyphomycoses have been associated with more than 100 species of fungi. These mycoses are more common in the tropics and are associated with the formation of subcutaneous inflammatory cysts. Entomophthoromycoses include diseases caused by species of *Basidiobolus* and *Conidiobolus*. Basi-

diobolomycosis is caused by *Basidiobolus ranarum*. Conidiobolomycosis (syn. rhinoentomophthoromycosis) is caused by *Conidiobolus coronatus*. Basidiobolomycosis has its highest prevalence in tropical Africa and southeast Asia and is a subcutaneous infection primarily of children and adolescents. Conidiobolomycosis occurs most frequently in adults in the tropical rain forests of West Africa and results in the tropical rain forests of West Africa and results in submucosal rhinosinusitis. Both entomophthoromycoses are similar in that they cause indolent infection with granulomatous changes in the skin and subcutaneous tissues without bone or systemic involvement.

Although histoplasmosis is seen throughout the world, African histoplasmosis is caused by *Histoplasma capsulatum* variety *duboisii*. This disease presents in African patients as mucocutaneous, subcutaneous, and bone lesions.

## CONCLUSIONS

Tropical mycoses are seen most often in persons who live in hot, humid climates, but travelers and workers from these parts of the world are presenting with increased frequency to dermatologists and other physicians who work in temperate climates. Global travel for vacation or employment also means that residents of temperate climates occasionally develop clinical manifestations of such infections weeks after returning home. Therefore it is important for physicians everywhere to be familiar with the mucocutaneous signs and symptoms of tropical mycoses and to be able to perform the proper diagnosis and initiate the appropriate therapy.

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