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Sixty year-old male with slowly expanding nodular plaque on the thigh

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CASE SUMMARY

History

A 60-year-old Chinese man presented to the NIH Dermatology Consultation Service for evaluation and treatment of a slowly expanding lesion on his right thigh. The lesion developed after a puncture injury from a splinter of the Burmese rosewood tree and enlarged slowly over the next 20 years. The site was reportedly asymptomatic and no systemic symptoms developed. Ten years after onset, the patient began treatment with oral itraconazole which continued for 2.5 years at a dose of 400–800 mg daily. The thigh lesion decreased in size and the erythema faded, however, the drug was discontinued prior to complete resolution due to hepatotoxicity. Several years after discontinuation of itraconazole, the plaque began to increase in size and became pruritic. At the time of evaluation, the patient was otherwise in good medical condition except for hypertension.

Physical Examination

The patient presented to the NIH with an amoeboid 17 cm x 13 cm plaque on the anterolateral right thigh (Fig 1, A). The plaque had a variegated appearance, including pale, atrophic, scarred areas; discrete, scaly nodules along the pink, lateral portions of the plaque; and a thicker, violaceous, papular and scaly, superomedial portion. No pustules or skin

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breakdown was present. There was no femoral or inguinal lymphadenopathy. The remainder of the physical examination was within normal limits.

Histopathology

Histopathologic examination of a 4-mm punch biopsy from the periphery of the plaque revealed granulomatous and acute inflammation in the upper dermis with overlying pseudoepitheliomatous hyperplasia. Pigmented sclerotic bodies (also called “copper pennies”, muriform cells or Medlar bodies) characteristic of chromoblastomycosis were present (Fig 2) within the abscess.

Significant Diagnostic Studies

Visible microscopic dematiaceous mold colonies were visible in tissue culture from at 8 days. The colonies were flat, velvety, and brown-black in color (both front and reverse) at 25° C (Fig 3, A).

Molecular identification of the isolate was performed at the NIH Clinical Center microbiology laboratory using the internal transcribed spacer (ITS) region (ITS1-5.8S rRNA gene-ITS2) of fungal DNA. PCR amplification and sequencing was accomplished using previously described reagents and cycling conditions with ITS1 and ITS4 primer pairs.¹ The isolate demonstrated 99.5% homology to *Fonsecaea pedrosoi* (AB114128).

Characteristic microscopic structures for *Fonsecaea pedrosoi* were seen at 15 days. Microscopic examination using lactophenol cotton blue staining demonstrated dematiaceous septate hyphae and conidiogenesis observed with the *Fonsecaea* species (*Fonsecaea* type, *Cladosporium* type, *Phialophora* type, and *Rhinocladiella* type; Fig 3, B). Susceptibility testing performed at the Fungal Testing Laboratory, San Antonio, TX, using Clinical and Laboratory Standards Institute methodology² resulted in minimum inhibitory concentrations for amphotericin B, caspofungin, itraconazole, posaconazole, terbinafine and voriconazole of 1.0, 1.0, 0.06, <=0.03, 0.015 and 0.06 µg/ml, respectively.

Immunologic evaluation, including dihydrorhodamine flow assay for chronic granulomatous disease, and serum immunoglobulins were within normal limits. Lymphocyte phenotyping revealed normal numbers of T and B lymphocytes, normal numbers of CD4+ T lymphocytes, and slightly decreased CD8+ T lymphocytes (279, normal range 344–011 cells/uL).

Diagnosis

Chromoblastomycosis (*Fonsecaea pedrosoi*)

FOLLOW-UP

Treatment was initiated with posaconazole 400 mg twice daily and heat therapy (heating pad applied to thigh 2 hours/day). Following two weeks of treatment, a peak serum drug level was 2.8 µg/mL. Although goal levels of posaconazole for the treatment of invasive mycoses have not been established, plasma levels greater than 0.7 µg/mL have been suggested for the treatment of invasive aspergillosis.³ The posaconazole dose was reduced to 300 mg twice daily and random serum levels collected one and five weeks after decreasing the dose were 2.1 and 1.7 µg/mL, respectively, which are similar to levels reported in a case of chromoblastomycosis due to *Cladophialophora carrionii* successfully treated with surgical excision and posaconazole 400 mg twice daily for six months.

Following eight months of treatment, nodularity and erythema of the plaque were significantly decreased. The patient currently continues on combination heat therapy and posaconazole treatment with progressive slow improvement in the plaque. (Fig 1, B).

DISCUSSION

Chromoblastomycosis is an uncommon cutaneous and subcutaneous infection caused by dematiaceous fungi. Although chromoblastomycosis has been reported worldwide, most cases occur in tropical and subtropical areas, including Latin America and Africa, a trend which reflects the natural habitat of fungal species in the Dematiaceae family.^{4–6} Infection occurs when a thorn or splinter of wood carrying the fungus penetrates and inoculates the skin. Lesions most often occur on the lower extremities of adult males (5:1 to 9:1), particularly low-income laborers and agricultural workers.⁷ Although immunocompromised populations are at increased risk of infection, most cases of chromoblastomycosis occur in otherwise healthy individuals.⁵

The clinical appearance of chromoblastomycosis is polymorphic. Chromoblastomycosis has been classified as verrucous, nodular, tumoral, cicatricial or plaque-type based on clinical presentation, but multiple morphologies may occur in advanced cases,^{5,8} and the clinical morphology of the lesions does not correlate with pathogen or disease course.⁷ Skin lesions usually begin as a papule and extend centrifugally over several years. The infection does not tend to extend deeply into muscle or bone,⁴ but disseminated cases have been reported and are thought to occur by self-inoculation from the original lesion or by lymphatic spread. A series of 100 cases from Brazil estimated a mean of 14 years before diagnosis.⁷ In another report from Jamaica, the mean duration of the disease before diagnosis was 8 years.⁹ This delay may reflect the asymptomatic nature of early lesions. Over time, however, patients ultimately begin to experience local pain or itching and in severe cases, edema, lymphedema and secondary bacterial infection. Co-infection with other deep fungal organisms and squamous cell carcinoma arising in chronic lesions have been described.^{4, 10} The differential diagnosis for chromoblastomycosis includes other infections such as sporotrichosis, leishmaniasis, blastomycosis, paracoccidioidomycosis, syphilis, mycobacterial infection, tuberculosis, and coccidioidomycosis, as well as noninfectious diseases such as sarcoidosis, verrucous carcinoma and cutaneous lupus.⁵

Chromoblastomycosis is caused by dematiaceous fungi, and the muriform cells (also known as “copper pennies,” “Medlar” or sclerotic bodies”) found on histology are unique to this infection. Sclerotic bodies are dark brown, spherical or polyhedral, thick-walled structures with horizontal and vertical septa. The presence of sclerotic bodies in the tissue confirms the diagnosis of chromoblastomycosis, but does not identify the fungus. The most common etiologic agent is *F. pedrosoi* (66–96% of cases), followed by *Cladophialophora carrionii* in temperate climates and *Phialophora verrucosa*.^{5,7} *Exophiala spinifera*, *Exophiala jeanselmei* and *Rhinocladiella aquaspersa* are also been associated with the disease.¹¹ Dematiaceous fungi are known as “black molds,” because they contain melanin, which is a presumed virulence factor for these molds. The exact pathogenic mechanism is not known, but the melanin may interfere with the oxidative burst of the phagocytic cells or bind to host hydrolytic enzymes.^{12,13}

Dematiaceous fungi also cause phaeohyphomycosis and eumycetomas.^{14,15} Eumycetomas are deep infections characterized by the triad of tumefaction, draining sinuses and grains. As with chromoblastomycosis, phaeohyphomycosis infections are often introduced by local trauma.^{12, 16} However, the presence of brown to black hyphae (instead of Medlar bodies) distinguishes phaeohyphomycosis from chromoblastomycosis.¹⁴ Phaeohyphomycosis infections may be superficial (including tinea nigra and black piedra), cutaneous, or

subcutaneous. Although phaeohyphomycosis can occur in immunocompetent patients, the likelihood of disseminated disease increases with immunosuppression,¹⁷ and the disease is often reported in solid organ transplant patients.¹⁴

Chromoblastomycosis infection results in a granulomatous reaction in the skin with neutrophils and macrophages. Although antibodies are generated, the bulk of the immune response is cell-mediated.¹¹ Infiltrating T-lymphocytes have been demonstrated at the periphery of the lesions. It is thought that treatment-refractory or more severe cases may be linked to a Th-2 type response.¹¹ A perigranulomatous fibrotic process is also often noted histologically.^{11, 18}

Despite medical and surgical therapy, cure of chromoblastomycosis infection is difficult and recurrences are frequent. As yet, no controlled therapeutic trials have been reported, so there is no medication or combination of medications considered the treatment of choice. *F. pedrosoi* infection and the presence of extensive dermal fibrosis are associated with recalcitrant disease due to low sensitivity to antifungal medications and decreased drug penetrance, respectively.¹⁹ Smaller lesions lend themselves to traditional excision with margins.^{8, 19} Mohs surgery has also been used, using the muriform cells to estimate the border of the lesion.²⁰ Electrodesiccation and curettage and carbon dioxide laser have also been attempted.²¹ Because the growth of most infections associated with chromoblastomycosis is slowed at 42–45°C, pocket warmers, local heating packs or electric blankets (thermotherapy) have been utilized with some success.^{21–24} Interestingly, cryotherapy has also been used, resulting in a cure in approximately 40% of cases.^{25, 26, 27}

Antifungal therapy for chromoblastomycosis consists of prolonged single agent or combination treatment. Although itraconazole and terbinafine are considered first-line agents due to their *in vitro* activities, clinical experience, and long-term safety, an optimal treatment regimen has not been established. Itraconazole is a fungistatic triazole which inhibits cytochrome P450 14 α -demethylase. The drug is better tolerated and safer than long-term ketoconazole, and has a lower minimal inhibitory concentration than fluconazole.²⁸ Itraconazole is generally used in daily doses of 200–400 mg for several months-years.²⁹ In Brazil, 8 of 30 patients achieved cure after an average of 10.9 months on itraconazole. In another series, 11 of 12 patients with mild disease had a complete response after an average of 12.9 months.³⁰ Voriconazole and posaconazole are second-generation triazoles with broad spectrum anti-fungal activity including *in vitro* activity against various dematiaceous fungi.¹² Posaconazole, a structural derivative of itraconazole, has demonstrated efficacy against chromoblastomycosis and refractory eumycetoma.^{31–34} Terbinafine has been used with doses ranging from 250–500 mg daily.⁸ In one series of 43 patients treated with 500mg daily for one year, 82.5% achieved clinical and mycologic cure.³⁵ Terbinafine is often given in combination with itraconazole as the two agents appear to have a synergistic effect.^{36, 37} Because of its recalcitrant nature, moderate-sized and larger chromoblastomycosis lesions often require combination treatment with systemic antifungal agents and medical therapy and other interventions. Due to prior hepatotoxicity with itraconazole, we chose an alternate agent. Because of the risk of photosensitivity associated with long-term voriconazole therapy, we chose posaconazole. Our group has extensive experience with long-term treatment with posaconazole with minimal hepatotoxicity or other adverse events. Our patient experienced gradual improvement with posaconazole in combination with heat therapy. Liver function tests have continued to be within normal limits.

KEY TEACHING POINTS

- Chromoblastomycosis is an uncommon subcutaneous infection caused by dematiaceous fungi. The most common infectious agent is *Fonsecaea pedrosoi* (66–96%).
- Given the reduced susceptibility of fungal species associated with chromoblastomycosis to standard antifungal therapy, timely and accurate speciation is essential to guide clinical management. However, conventional culture-based phenotypic identification can be slow and difficult. Fungal isolate sequencing utilizes fungal DNA from initial culture growth to permit rapid species identification.
- The infection is chronic and difficult to treat and well-designed interventional studies are lacking. If the lesion cannot be removed by surgical excision, medical therapies may be of benefit; however, recurrence is common even after twelve months or more of antifungal therapy.

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ABBREVIATIONS

ITS Internal transcribed spacer

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Fig 1.
A, Large plaque on the anterolateral aspect of the right thigh. There is evidence of chronic changes with central scarring and a nodular, erythematous border. **B,** Follow-up after 7 months on combination treatment with oral posaconazole and heat therapy.

Fig 2. Histopathology of chromoblastomycosis. Pigmented sclerotic bodies are found within the abscess and granulation tissue in the dermis (Hematoxylin-eosin stain; original magnification: x 400)

Fig 3.
A, Velvety, dark dematiaceous colony growth on Sabouraud dextrose agar. **B,** Lactophenol cotton blue preparation of *Fonsecaea pedrosoi* colony (x 400).