Pseudallescheriasis as an Aggressive Opportunistic Infection in a Bone Marrow Transplant Recipient

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• *Pseudallescheria boydii* is a low-virulence fungus that is the main causative agent of posttraumatic mycetoma in a nonimmunocompromised host. Immunocompromised patients are at high risk for locally invasive or disseminated *Pseudallescheria* infection. However, aggressive opportunistic infections due to *P boydii* are reported infrequently because it morphologically resembles other fungi, especially *Aspergillus* species, on tissue histology; therefore, such infections are not identified and treated properly. We report a case of disseminated *P boydii* infection in a patient following bone marrow transplantation. The identity of the fungus was not recognized until microbiologic culture results became available. Our case illustrates the importance of recognizing this fungus as an opportunistic infection in immunocompromised patients, as well as the need for culture of biopsy material for proper identification so that appropriate therapy can be instituted.

*(Arch Pathol Lab Med. 2002;126:207–209)*

**Pseudallescheria boydii**, previously categorized in the genera *Allescheria*, *Monosporium*, and *Petriellidium*, is the perfect (sexual) form of *Scedosporium apiospermum*. It is a ubiquitous soil-inhabiting organism with worldwide distribution and is a well-known causative agent of mycetoma.1 It rarely occurs at extracutaneous sites. However, an increasing number of cases of disseminated pseudallescheriasis has been observed in immunocompromised patients due to increased incidence of human immunodeficiency virus infection, antineoplastic or immunosuppressive medication, and bone marrow or solid organ transplantation.2–4 Infection due to *P boydii* is often resistant to common antymycotic drugs, such as amphotericin B and fluconazole.1 Failure to recognize this fungus as an aggressive opportunistic infection because of the morphologic resemblance of *P boydii* to other fungi, such as *Aspergillus* species and *Fusarium* species, and the time required for culture and identification of the organism may delay appropriate therapy and result in a fatal outcome. We report a case of *P boydii* infection in a patient who received an allogenic stem cell transplant for recurrent multiple myeloma.

**REPORT OF A CASE**

The patient was a 49-year-old man diagnosed with stage III-A multiple myeloma, IgA type, in July 1997. He received 4 cycles of VAD (vincristine, doxorubicin, and dexamethasone) and radiation therapy to the pelvis and sacrum before undergoing autologous stem cell transplantation in February 1998. The patient experienced a relapse of multiple myeloma in August 1999, and he received an allogenic stem cell transplant on October 11, 1999. One week later, he developed fever, palmar erythema, and hyperpigmented papules on the dorsum of the left foot. Fungal infection and acute graft versus host disease were suspected. Multiple blood cultures were negative for bacterial or fungal growth. Following an inconclusive biopsy of the palmar lesion, a diagnosis of acute graft versus host disease was confirmed on October 28 by a rectal biopsy. A 3-mm skin punch biopsy from the left dorsal foot lesion on October 19 showed histologic features (see below) thought to be morphologically consistent with *Aspergillus* infection. The patient was started on amphotericin B. After the fungal organism was identified as *P boydii* from culture on October 25, miconazole therapy was initiated, but it did not ameliorate his infection and he was started on itraconazole. His condition continued to deteriorate, and the ulcer of the left dorsal foot grew larger. To evaluate for possible amputation, a second biopsy of the left foot ulcer was performed on November 3. He developed multiple organ failure and died on November 4. A postmortem examination was performed.

**PATHOLOGIC FINDINGS**

The first skin biopsy of the left foot showed a small abscess in the deep dermis (Figure 1, A) containing numerous fungal hyphae. Periodic acid–Schiff and methenamine silver stains disclosed septate, hyaline, and branching hyphae, which were 3 to 7 μm in diameter, and a few spores (Figure 1, B). The hyphae branched mostly at 45° angles, with occasional 90° branching. A portion of the skin biopsy was submitted for microbiological study. The specimen was inoculated onto Sabouraud dextrose agar and brain-heart infusion agar slants. After incubation at 30°C for 7 days, the colonies demonstrated gray aerial mycelium. Microscopically, the hyphae were hyaline and septate. Small round conidia were attached to short simple conidiophores, resembling lollipops. Cleistothecia were observed after 2 weeks of incubation on potato dextrose agar and cornmeal agar (Figure 1, C). The cleistothecia were dark brown and contained numerous ovoid ascospores. According to these morphologic features, the fungus was identified as *P boydii*.

The second biopsy of the same area showed extensive necrosis of the skin and subcutaneous tissue associated with extensive fungal growth forming multiple layers...
Figure 1. First biopsy of the left foot lesion. A, Low-magnification view showing a small abscess in the deep dermis (hematoxylin-eosin, original magnification ×160). B, Higher magnification view disclosing numerous septate and branching hyphae. The hyphal branches occur mostly at 45° angles with occasional 90° angles. A few rod-shaped spores are also noted (methenamine silver, original magnification ×200). C, Culture from the same lesion showing cleistothecia, which were dark brown (aniline blue, original magnification ×500).

Figure 2. The second biopsy of the left dorsal foot ulcer showing multilayered fungal growth with hypercellular zone alternating with hypocellular zone (methenamine silver, original magnification ×160).

Figure 3. Lung at autopsy. A, Gross photograph showing multiple small nodular lesions (arrows), some of which are hemorrhagic. B, Histology of the nodular lesion showing vascular invasion by the fungus with associated thrombosis (methenamine silver, original magnification ×160).
with hypercellular and hypocellular zones. Methenamine silver staining highlighted fungi that were morphologically identical to those of the first biopsy. Vascular invasion of the organism with thrombosis was also present (Figure 2).

At postmortem examination, multiple hemorrhagic nodular lesions were present in the lungs (Figure 3, A) and in the gray and white matter of the cerebrum, as well as deep within the ulcer of the left foot. Microscopically, extensive tissue invasion by branching fungal hyphae, including vascular invasion with thrombosis, was evident (Figure 3, B). Pseudallescheria boydii was identified in the cultures of the lung and foot lesions.

**COMMENT**

Pseudallescheria boydii is best known for causing mycetoma, or "Madura foot," which is a chronic infection of the skin and subcutaneous tissues, often with multiple draining sinuses. Extracutaneous infection is extremely rare in immunocompetent hosts. However, the use of corticosteroids, immunosuppressive or antineoplastic medication, bone marrow or solid organ transplantation, and human immunodeficiency virus infection have increased the occurrence of disseminated pseudallescheriasis.3,4,6,7 The portal of entry could be lung, paranasal sinuses, or skin by traumatic inoculation.4 In our case, the skin lesion in the left leg was the apparent source of disseminated infection.

As seen in our patient, the microscopic findings in invasive pseudallescheriasis are characterized by mycotic thrombosis, resulting in necrosis or infarct, similar to findings in aspergillosis. In areas of necrosis, hyphae are often fragmented and basophilic. The hyphae have a random, haphazard pattern of branching rather than the progressive, arborizing pattern of the branching characteristics of Aspergillus infections. Also, hyphae of P boydii do not have the fragile, "crumpled," or "twisted ribbon" appearance of Zygomycetes, which may also have rare septation.9 However, Pseudallescheria and Aspergillus species cannot be reliably differentiated on histologic sections unless characteristic asexual fruiting bodies are present.4 With adequate exposure to air, Aspergillus species can produce radiating metulae and chains of round spores, in contrast to the unicellular oval conidia produced by P boydii.9,10,11 In addition, the conidia of P boydii are more oval and have a truncated end compared with those of Aspergillus.9 Unfortunately, the characteristic Pseudallescheria conidia are rarely present in deep tissue sections; they have been described in pulmonary fungomas (fungus balls) and endocardial thrombi.4 Our case illustrates the difficulty in identifying this fungus based on histology alone. It is important to maintain a high index of suspicion for this organism when evaluating fungal infection in immunocompromised patients. It is also important to perform a microbiologic study simultaneously to correctly identify the organism in order to provide prompt and appropriate treatment.7 Alternatively, identification of Aspergillus infection using a monoclonal immunoperoxidase technique on paraffin section12 and tissue diagnosis of pseudallescheriasis by immunofluorescent methods on formalin-fixed and paraffin-embedded tissue are now available. These techniques may be used to improve the histologic diagnosis of this fungal infection.

A prompt and accurate diagnosis of invasive fungal infection is of great importance because the choice of treatment for systemic Aspergillus infection is amphotericin B or itraconazole, whereas P boydii is moderately resistant to amphotericin B and is more effectively treated with imidazole derivatives, such as itraconazole and miconazole.13 Without appropriate therapy, invasive P boydii infection in immunocompromised patients, as in our case, may have a rapid fatal course.

**References**


