

Scytalidium dimidiatum and *Lecythophora hoffmannii*: Unusual Causes of Fungal Infections in a Patient with AIDS

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Immunocompromised patients are susceptible to infections by fungi that seldom cause disease in humans. We describe a human immunodeficiency virus-infected patient who had simultaneous infections with two fungi which are rare causes of serious infection: *Lecythophora hoffmannii*, causing chronic sinusitis, and *Scytalidium dimidiatum*, causing skin lesions, lymphangitis, and lymphadenitis. The clinical and pathologic findings are discussed.

Fungal infections are common in patients with AIDS, with the majority predictably caused by *Candida albicans*, *Cryptococcus neoformans*, and the endemic dimorphic fungi such as *Histoplasma capsulatum* and *Coccidioides immitis*. Infections due to other fungi are much less frequently described, although the antemortem incidence of aspergillosis quoted in a recent review by Khoo and Denning (8) ranges from 1.9 to 8.6% in various retrospective studies, with the lung being the most frequent site of involvement. The yeasts *Saccharomyces cerevisiae*, *Rhodotorula rubra*, and *Candida glabrata*; a variety of molds, including the zygomycetes genera *Rhizopus*, *Absidia*, and *Cunninghamella*; and other fungi, including *Scedosporium apiospermum* and its teleomorph *Pseudallescheria boydii*, *Bipolaris* spp., and *Alternaria* spp., have rarely been reported as causing systemic infections (2).

We describe a patient with AIDS who was infected with two opportunistic fungal pathogens: *Scytalidium dimidiatum*, a dematiaceous hyphomycete associated with wood and soil, and *Lecythophora hoffmannii*, a plant pathogen classified with the dematiaceous fungi but often lacking a dematiaceous appearance both in vivo and in vitro (15).

CASE REPORT

A 44-year-old Caucasian homosexual man was diagnosed with human immunodeficiency virus (HIV) infection in October 1989 and developed *Pneumocystis carinii* pneumonia in December 1992. Sequential antiretroviral therapy included zidovudine, zalcitabine, and didanosine; however, the CD4 count remained below 50×10^6 /liter. In January 1993 the patient developed an intermittent productive cough with dyspnea. A thoracic computed tomography scan was consistent with bilateral cylindrical bronchiectasis. Following the onset of facial pain and nasal discharge, a sinus X ray was performed and maxillary sinusitis was confirmed.

In February 1993, the cough worsened and sputum culture grew *Aspergillus fumigatus* and *S. apiospermum*. Itraconazole treatment (400 mg daily) was commenced. One month later,

the symptoms of sinusitis became more severe. Bilateral antral aspiration and lavage were performed under general anesthesia. Markedly thickened sinus mucosa was demonstrated. Microscopy of antral washings demonstrated occasional polymorphonuclear leukocytes but no organisms were seen. *L. hoffmannii*, resistant to amphotericin B, flucytosine, ketoconazole, and fluconazole, was subsequently isolated from the sinus aspirate. Symptoms related to the chronic sinusitis were relieved after surgical drainage. However, in August 1993, the sinusitis again worsened, and a computed tomography scan of the affected area revealed extensive erosive pansinusitis. Another lavage was performed, which resulted in an improvement in symptoms, and *L. hoffmannii* was again isolated.

Lesions resembling Kaposi's sarcoma (KS) developed in August 1993 and were treated with vincristine and bleomycin. Disseminated *Mycobacterium avium* complex infection was diagnosed in October 1993 and was treated with rifabutin, ethambutol, and clarithromycin. Cytomegalovirus retinitis developed and responded to ganciclovir treatment followed by maintenance therapy. Local radiotherapy was administered in May 1994 for progressive KS-like lesions in the inguinal region.

In June 1994, the patient was admitted to hospital with back pain and peripheral edema. Physical examination demonstrated a tender mass in the left inguinal region with overlying inflammation and oozing and marked scrotal edema. Purplish, indurated, weeping lesions were noted in the right inguinal region and over both feet and toes. The clinical diagnosis was cellulitis and lymphadenitis secondary to radiotherapy. Treatment was commenced with intravenous flucloxacillin and gentamicin with some improvement, and the patient was discharged several days later. However, 1 week later he was readmitted with increasing left inguinal pain. Examination revealed more marked inflammation with probable abscess formation and increased scrotal and left leg edema (Fig. 1A). The purple, indurated skin lesions were again noted over the inguinal regions, both feet, and the right toes (Fig. 1B).

Initial investigations showed a hemoglobin concentration of 106 g/liter (normal, 130 to 180), an absolute neutrophil count of 2.2×10^9 /liter (normal, 2.0×10^9 to 7.5×10^9), a platelet count of 100×10^9 /liter (normal, 150×10^9 to 400×10^9), an

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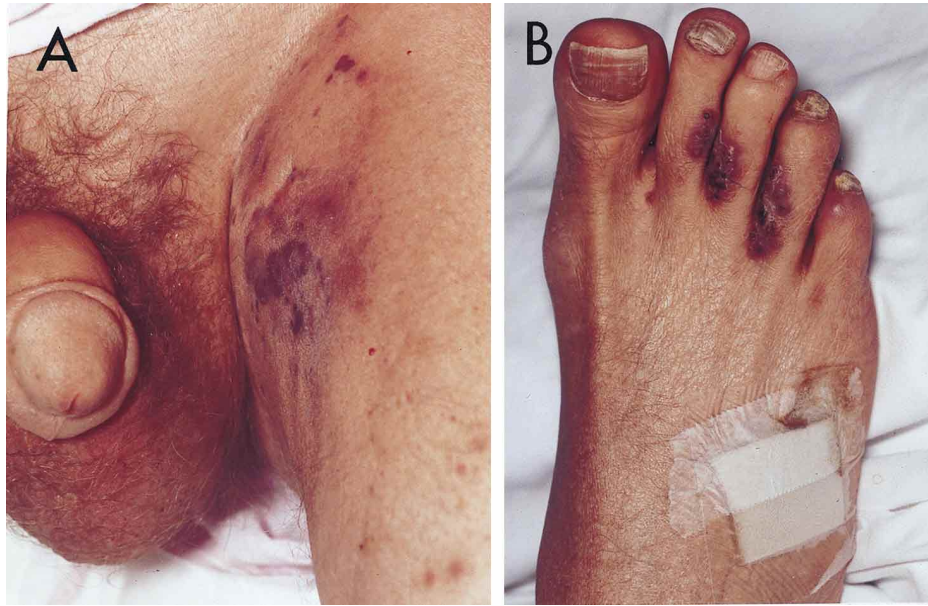


FIG. 1. (A) Indurated purplish lesions associated with inguinal lymph adenopathy and edema of the penis and scrotum. (B) Lesion on the right foot (biopsy of third toe).

alkaline phosphatase concentration of 418 U/liter (normal, 30 to 100), a creatinine concentration of 0.13 mmol/liter (normal, 0.06 to 0.12), an aspartate aminotransferase concentration of 103 U/liter (normal, <30), a gamma glutamyl transferase concentration of 199 U/liter (normal, <35) and a CD4⁺ cell count of <10 × 10⁶/liter. An abdominal ultrasonogram revealed moderate splenomegaly. In view of the poor response of the inguinal lymphadenitis and cellulitis to conventional antibiotics, a fine-needle aspiration biopsy of the inguinal lymph node and a surgical biopsy of the right third toe lesion were undertaken.

S. dimidiatum grew from both sites, and histology confirmed the presence of numerous fungal hyphae and purulent granulomatous inflammation in both the surgical biopsy and the fine-needle aspiration specimens. The organism was resistant to itraconazole in vitro. Amphotericin B therapy was commenced, and the skin lesions, left inguinal lymphadenitis, and edema improved gradually. A cumulative dose of 1 g of amphotericin B was administered, and the therapy was switched to ketoconazole. However, the patient's general condition and nutritional status slowly deteriorated. The patient decided to withdraw from active treatment and was transferred to a hospice for palliative care. He died 3 weeks later, as a result of end-stage HIV infection. A postmortem examination was not performed, but at death there was no clinical evidence of active fungal infection.

MATERIALS AND METHODS

A fine-needle aspiration of the left inguinal lymph node and a surgical biopsy of the toe were performed. Smears and tissue sections were stained by Gram stain, hematoxylin and eosin, Giemsa stain, and methenamine silver stain. The aspirate and tissue were cultured by standard techniques on blood agar, MacConkey agar, brain heart infusion agar, and Sabouraud's dextrose agar (Oxoid, Basingstoke, England).

The frontal sinuses were aspirated by an aseptic technique, and Gram stain and culture were performed as detailed in the previous paragraph. Sputum specimens were obtained by standard methods, and Gram stain confirmed the lack of salivary contamination. Culture on blood agar (Oxoid) and chocolate agar (Oxoid) with 5 µg of bacitracin/ml was performed. Fungal sensitivity tests were performed by a disc diffusion method with Neo-Sensitabs (Rosco, Taastrup, Denmark) on 90-mm-diameter plates containing 20 ml of yeast nitrogen base agar (Difco, Detroit, Mich.). The method is based on that of Casals and Pringler

(1) with the modification that 1.0 ml of a McFarland no. 4 suspension was added to 20 ml of yeast nitrogen base agar (Difco) supplemented with asparagine rather than swabbing the plates with the saline suspension. The antifungal agents tested were amphotericin B, flucytosine, ketoconazole, fluconazole, and itraconazole.

RESULTS

Mycology. Neither fungus could be identified from the standard isolation media. For identification to the species level, slide cultures were prepared on potato dextrose agar, cornmeal agar, and 2% agar. *L. hoffmannii* produced pink colonies with a tan reverse on Sabouraud's dextrose agar. On potato dextrose agar, the colonies became darker olivaceous in color with age. Microscopy was characterized by packed strands of hyphae with simple, smooth, hyaline conidiophores. Phialides were flask shaped to cylindrical, single, and without collarettes. Conidia were hyaline, smooth, and slightly curved (0.6 to 2.3 by 2.2 to 6.0 µm) and tended to aggregate in clusters at the tip of the phialides (Fig. 2A).

S. dimidiatum produced dark brown to black colonies on all media. The microscopy showed two types of hyphae, the younger being hyaline, branched, and septate. The older hyphae were dark brown, branched, and septate and divided into dark brown, septate (zero to one), thick-walled arthroconidia (4 to 16 by 8 to 9 µm) which arose from disarticulating hyphae (Fig. 2B). This is the synanamorph of *Natrassia mangiferae* (17), which requires more specialized conditions for the production of pycnidia. These were produced after 3 weeks of incubation on cornmeal agar in daylight and at room temperature. The conidia in these structures are slow to form, being initially hyaline to pale brown and eventually mid-brown with one or two septa, the median cell being larger than the two end cells.

These isolates have been retained in the collection of the Australian National Reference Laboratory in Medical Mycology (AMMRL) as *L. hoffmannii* AMMRL 148.02 and *S. dimidiatum* AMMRL 00.1.

Susceptibility testing. *L. hoffmannii* was resistant to all antifungal agents tested, with no zone recorded for amphotericin B, ketoconazole, itraconazole, fluconazole, or flucytosine.

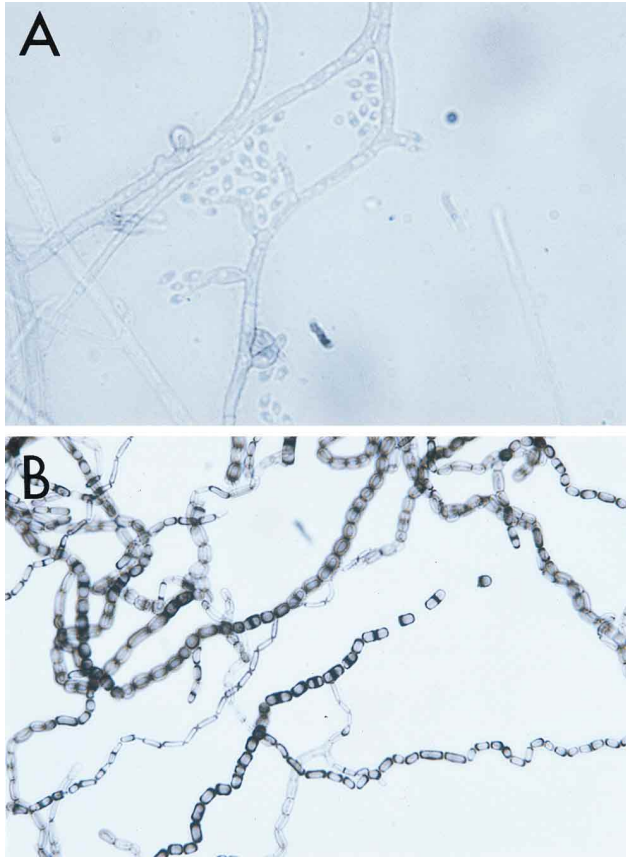


FIG. 2. (A) Microscopic appearance of *L. hoffmannii* showing flask-shaped to cylindrical phialides with curved hyaline conidia at the tips of the phialides. Magnification, $\times 924$. A lactophenol cotton blue preparation is shown. (B) Microscopic appearance of *S. dimidiatum* showing dark brown, thick-walled arthroconidia. Magnification, $\times 462$. A lactophenol cotton blue preparation is shown.

Zone diameters for *S. dimidiatum* were as follows: amphotericin B, 31 mm (sensitive); flucytosine, 46 mm (sensitive); fluconazole, 18 mm (sensitive); ketoconazole, 18 mm (sensitive); and itraconazole, no zone (resistant).

Histology. Biopsy of the toe revealed purulent granulomatous inflammation of the dermis. Special stains, including Gomori's methenamine silver stain, demonstrated numerous fungal elements in the granulomata (Fig. 3). Stains for acid-fast bacilli were negative, and the histological changes were not consistent with KS. The fine-needle aspiration of the inguinal lymph node contained macrophages, granulomatous tissue fragments, and plentiful septate branching fungal structures.

DISCUSSION

The spectrum of human mycoses continues to expand dramatically with fungi that were rarely considered to be human pathogens now recognized as causing disease, particularly in immunocompromised patients. This paper describes a severely immunodeficient HIV-infected patient who had significant infection with the rare opportunistic pathogens *L. hoffmannii* and *S. dimidiatum*. This is only the second documented case of significant *L. hoffmannii* infection and the first case of chronic, recurrent sinusitis caused by this organism.

L. hoffmannii (van Beyma) Gams et McGinnis is rarely encountered as a human pathogen. It is in fact a group of related taxa rather than a single species (5). Most reports of pathogenicity have been due to a closely related species, *Lecythophora*

mutabilis (van Beyma) Gams et McGinnis, which has been described as causing infective endocarditis (13, 16). *L. hoffmannii* has been isolated from a gluteal abscess in a 73-year-old patient (14) who was not immunocompromised but who developed an abscess at the site of an intramuscular injection given in Spain 4 months earlier.

The genus *Scytalidium* currently accommodates both lightly and darkly pigmented fungi. *S. dimidiatum* (Penzig) Sutton et Dyko is the synanamorph of a coelomycete known as *Natrassia mangiferae* (Sydow et Sydow) Sutton et Dyko, a plant fungus which grows on stone fruit and was previously known as *Hendersonula toruloidea* Natrass. *S. dimidiatum* (Syn: *S. hyalinum* and *S. lignicola*) was reclassified by Sutton and Dyko (17) in 1989 and is the form of the fungus found on routine culture media. *S. hyalinum* is thought to be a pigment-deficient variant of *S. dimidiatum* (17). There have been a number of reports of *S. dimidiatum* infection of skin and nails. Moore (12) has reviewed these infections and reported that most originate in tropical and semitropical regions such as South America, southeast Asia, and west Africa. In temperate zones infections generally occur in immigrants from areas of endemicity. Kane et al. (7) described the first indigenous Canadian case in 1990, and Frankel and Rippon reported three cases of dermatomycosis in the temperate regions of the United States (4). There has been only one report of a case in Australia (10) in which *S. hyalinum* was isolated from the toenail of a patient with chronic onychomycosis. Levi and Smith (9) reported a case of posttraumatic wound infection due to *S. dimidiatum* after the patient struck the thumb web with a wooden sledgehammer. It was postulated that the infection was introduced from contaminated soil present on the sledgehammer.

Although superficial infections with *S. dimidiatum* are well described, systemic infections are rare and include a subcutaneous mycotic abscess in an American diabetic patient (3) and sinusitis associated with maxillary necrosis in a French diabetic patient (11). The lymphadenitis, cellulitis, and skin lesions seen in our patient have not been previously described. It is postulated that the foot was the portal of entry in this patient, as he had extensive scaling lesions from which *S. dimidiatum* was subsequently cultured and breaches in the integrity of the skin caused by KS. Lymphangitic spread to the inguinal lymph nodes resulted in lymphangitis and lymphadenitis. The toenails, which appeared abnormal, were cultured in September 1993. Moderate numbers of fungal hyphae were seen, but the



FIG. 3. Fine-needle aspiration from the left inguinal lymph node demonstrating fungal hyphae. A Gomori's methenamine silver stain is shown. Magnification, $\times 924$.

isolate was discarded by the laboratory as a probable contaminant without complete identification.

The source of *L. hoffmannii* and *S. dimidiatum* infection in this patient is not known. He lived and worked in an urban area, and his only overseas travel was to Germany as part of his employment. He had no known contact with immigrants from areas of endemic *S. dimidiatum*, and as previously stated, there has only been one other description of isolation of this fungus from an Australian patient.

S. dimidiatum is inhibited by cycloheximide (6), a polyene antibiotic which is often incorporated into standard fungal isolation media for dermatophytes to prevent the growth of contaminants. This may partly explain the relative rarity of clinical isolation of this organism, as a cycloheximide-free medium such as Sabouraud's dextrose agar must be used to isolate *S. dimidiatum*.

This paper expands the spectrum of recognized fungal pathogens in HIV-infected patients and highlights the fact that no fungus should be automatically considered to be a contaminant in an immunocompromised patient.

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