Cutaneous Aspergillosis and Acquired Immunodeficiency Syndrome

George J. Murakawa, MD, PhD; Jeff D. Harvell, MD; Paul Lubitz, MD; Sanford Schnoll, MD; Sue Lee, MD; Timothy Berger, MD

Background: Primary cutaneous aspergillosis is an uncommon finding in patients with acquired immunodeficiency syndrome (AIDS); only 13 cases have been reported in the literature.

Observations: We describe 11 patients with primary cutaneous aspergillosis and AIDS. There does not seem to be an age, sex, race, or human immunodeficiency virus risk factor predisposition. This is a late manifestation of AIDS; patients typically have low CD4 counts (<0.050 × 10⁹/L [<50/µL]) and other AIDS-defining illnesses. The most frequent presentation is in patients with cytomegalovirus disease and neutropenia caused by ganciclovir therapy. Lesions developed at the site of occlusive dressings for an indwelling intravenous catheter site in 10 patients. Neutrophil counts may be normal at the time of diagnosis. A minor presentation is in the patient without neutropenia as a result of traumatic inoculation. Histological findings and/or culture results are required for diagnosis. Patients develop cutaneous lesions despite prophylactic therapy with fluconazole. Lesions can be treated with excision and lifelong therapy with itraconazole.

Conclusion: Because of the potential morbidity and mortality of cutaneous aspergillosis, a high level of suspicion and prompt institution of therapy is required.

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ASPERGILLUS SPECIES are ubiquitous organisms.¹ Invasive aspergillosis is primarily a disease of the modern medical era, presenting as either localized or disseminated disease. It is the second most common cause of opportunistic fungal infections, surpassed only by Candida species. The main factors involved in the pathogenesis of invasive aspergillosis are suppression of the host’s immune response and a local point of entry.

Patients with cutaneous aspergillosis can present with either primary or secondary skin lesions.²,³ Primary cutaneous aspergillosis arises either from direct physical inoculation, as in a penetrating wound, or at the site of an occlusive dressing at an indwelling catheter.⁴ The latter group includes patients who are typically immunocompromised, eg, from malignancies or organ transplantation, or premature infants.⁵,¹⁰ Construction sites and contaminated air vents have been associated with epidemics in hospitals.⁶,⁷

In contrast, patients with secondary cutaneous aspergillosis develop skin lesions from either direct extension, usually on the chest wall in patients with pulmonary aspergillosis, or from hematogenous dissemination.¹¹,¹² The respiratory tract is the most common portal of entry in patients with disseminated disease.¹ The clinical course is usually fulminant, with death occurring within 2 weeks.

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Herein, we report 11 cases of primary cutaneous aspergillosis and acquired immunodeficiency syndrome (AIDS) and review the literature.¹³-²¹

RESULTS

The Table lists our patients and their clinical characteristics. Our patients ranged in age from 32 to 58 years (median age, 40 years). All of our patients were homosexual white men who had preexisting or coexisting opportunistic infections or Kaposi sarcoma. The CD4 T-helper cell counts ranged from 0 to 0.013 × 10⁹/L (0-13/µL) (median count, 0.004 × 10⁹/L) in the patients with available data. At least 4 patients were receiving highly active antiretroviral therapy, and an additional 4 pa-
PATIENTS, MATERIALS, AND METHODS

All patients included in this study were diagnosed with cutaneous aspergillosis and AIDS at the University of California, San Francisco dermatology clinics or through the dermatopathology services at the University of California, San Francisco hospitals between 1993 and 1997. Patient records and microscopic slides were reviewed. All patients were ambulatory at the time of diagnosis, and no common epidemiologic source was identified.

Hematoylin-eosin–stained sections (supplemented with periodic acid–Schiff or Gomori methenamine silver–stained sections) were reviewed by light microscopy. The histopathologic features of the 11 cases of primary cutaneous aspergillosis were compared with 4 cases of secondary cutaneous aspergillosis. All 4 were immunocompromised on the basis of malignancy and chemotherapy (not human immunodeficiency virus [HIV]), and had clinical evidence of fungal pneumonia at the time of cutaneous biopsy.

tients were being treated with one or more antiretroviral nucleoside inhibitors. At least 8 of our patients were neutropenic (absolute neutrophil count <1 × 10^9/L [<1000/µL]) or receiving granulocyte colony-stimulating factor. Ganciclovir was the cause of neutropenia in each of these cases. At least 9 of our patients were receiving fluconazole at the time of diagnosis; 1 patient was taking itraconazole.

Ten of 11 patients developed cutaneous lesions at the dressing site of an indwelling intravenous catheter—either a peripherally inserted central catheter or a Hickman catheter line. The other patient developed primary cutaneous aspergillosis at the site of trauma. All lesions were asymptomatic. The morphological characteristics of the cutaneous lesions were described as nodules, fluctuant papules, deep-seated pustules, vesiculopustular plaques, and nonhealing ulcers. Figure 1 shows the cutaneous lesions, ulcers, at the site of an indwelling catheter (patient 3). The diagnosis was made or confirmed by histological analysis or culture findings of biopsy specimen obtained from lesions. Aspergillus fumigatus grew from the cultures of 6 patients, an unidentified species from that of another patient, and culture findings were negative in 2 cases (no levels were drawn); subsequent to lesion excision, the dose was increased to 200 mg three times daily. Patient 10 was treated only by surgical excision because his CD4 count rose from 0 to 0.386 × 10^9/L after initiation of treatment with highly active antiretroviral medications, and his lesions have not recurred.

Histologically, lesions of primary cutaneous aspergillosis demonstrated either superficial or superficial and deep areas of dermal necrosis containing septate hyphae with acute-angle branching. Necrotic zones were surrounded by a moderate polymorphonuclear inflammatory cell infiltrate and abundant nuclear dust (Figure 2). A few macrophages were evident, and multinucleated giant cells never appeared. Fungal hyphae could be seen in hematoxylin-eosin–stained sections, but staining with periodic acid–Schiff or Gomori methenamine silver highlighted their morphological characteristics, including septations (Figure 2). In 1 case, there was marked pseudopitheliomatous hyperplasia and syringosquamous metaplasia. Two cases exhibited masses of hyphae surrounded by remnants of follicular epithelium. Cytomegalovirus nuclear and cytoplasmic inclusions were identified as incidental findings in 2 cases. There was no correlation between positive culture findings and the density of organisms in the histological sections.

The 4 cases of secondary cutaneous aspergillosis differed histologically from the cases of primary cutaneous aspergillosis. In secondary cutaneous aspergillosis, the bulk of inflammation tended to reside in the deep reticular dermis and subcutaneous fat; in the primary cutaneous cases, the bulk of inflammation was either superficial or superficial and deep (Figure 3). One histological feature unique to the secondary cases was the finding of dilated and thrombosed reticular dermal blood vessels, whose lumens were expanded by masses of hyphae. Although blood vessel thrombosis occurred in some primary cases, masses of hyphae filling vessel lumens were never seen.

Primary cutaneous aspergillosis is an uncommon late-stage manifestation in patients with AIDS. All of our patients had low CD4 T-helper cell counts (<0.013 × 10^9/L) and other AIDS-defining diseases. We report 11 new cases in addition to the 13 previously reported cases (Table 1).

Primary cutaneous aspergillosis can be divided into 3 groups: cases occurring (1) in the setting of secondary colonization of burns or other wounds; (2) at the site of traumatic inoculation; or (3) at the site of an intravenous line in immunocompromised hosts. Each of these has been described in patients with AIDS. The first 2 groups may be seen earlier in the disease; the third is by far the most frequent and occurs in patients with late-stage AIDS. Patients who develop cutaneous aspergillosis from penetrating trauma may not be neutropenic.

Neutropenia and occlusive dressings at the site of an indwelling intravenous catheter or trauma were the principal risk factors for primary cutaneous aspergillosis in our...
patients. Patients developed cutaneous aspergillosis despite receiving supplemental granulocyte colony-stimulating factor and having relatively normal polymorphonuclear leukocyte counts, suggesting that the host's neutrophils may be defective or that the aspergillosis manifested during transient periods of neutropenia. This is in marked contrast to neonatal patients, whose lesions resolve spontaneously with increasing white blood cell counts. Roilides et al tested the antifungal activity of neutrophils from several pediatric HIV-positive patients with low CD4 counts and found that they were diminished.

Histologically, lesions of primary cutaneous aspergillosis demonstrated masses of septate hyphae and extensive dermal necrosis with a surrounding cuff of polymorphonuclear leukocytes and nuclear debris (Figure 2). Chronic inflammation in the form of macrophages and multinucleate giant cells was minimal to nonexistent. As compared with cases of secondary cutaneous aspergillosis in
immunocompromised, non–HIV-infected patients with Aspergillus pneumonia, there were several histological differences. In primary cutaneous infections, the epicenter of inflammation was in the superficial dermis, and thrombosed vessels did not have intravascular hyphae. In contrast, in secondary cutaneous aspergillosis, the epicenter of inflammation was more deep seated and involved only the reticular dermis or subcutaneous fat (Figure 3), and blood vessels in the deep reticular dermis were dilated and thrombosed with masses of hyphae expanding their lumens. We suspect that these findings reflect the fact that in secondary skin involvement, the route of dissemination is primarily through blood, with fungal organisms becoming lodged in dermal vessels of moderate caliber located in the deep dermis and subcutaneous fat. Since Pseudallescheria boydii (Scedosporium apiospermum) and Fusarium species can display nearly identical acute angle-branching septate hyphae, the histological findings of our culture-negative cases were consistent with, but not entirely diagnostic of, cutaneous aspergillosis. However, there is a strong correlation of Aspergillus species infections associated with intravenous catheter sites and not with P. boydii and Fusarium species, suggesting that Aspergillus species is the cause in culture-negative cases. A combination of surgical excision and itraconazole therapy was effective for all of our patients. Itraconazole alone was ineffective, since patient 1 developed lesions despite prophylactic itraconazole therapy and patient 3 had recurrence after itraconazole treatment was temporarily discontinued. Two of our patients died within 3 months from non-aspergillosis-related diseases. In the patients from the literature, 4 patients died within a few months; 2 patients had disseminated aspergillosis.14,18 Fluconazole did not prevent cutaneous aspergillosis—at least 9 of our patients and 3 patients in the literature were taking fluconazole at the time of diagnosis. A single patient was taking itraconazole at the time of diagnosis. Only amphotericin B and itraconazole have activity against Aspergillus, with only about a 30% to 40% success rate.1,23 Few itraconazole-resistant Aspergillus strains have been isolated.24 Itraconazole is given with a loading dose of 600 mg/d for 4 days and then 400 mg/d as a maintenance dose indefinitely.

Cutaneous findings for primary aspergillosis are characteristic. Biopsy specimens from the lesions should be taken for histological and culture analysis, and a potassium hydroxide test performed. After 1 week, if organisms are seen histologically, empiric therapy can be started, pending microscopic therapy. While other fungi appear similar, they are much less common and are not associated with intravenous sites. Cases in which organisms are not identified should undergo another biopsy of lesions and have the specimens sent for bacterial, mycobacterial, and fungal culture studies. Once diagnosis is made, therapy should be instituted immediately—direct surgical excision with margins free of an inflammatory infiltrate in combination with administration of
systemic antifungal agent(s) (amphotericin B with or without 5-flucytosine, and/or itraconazole). Patients with advanced AIDS may require lifelong suppressive therapy. If patients do not respond to oral itraconazole therapy, serum itraconazole levels must be checked to ensure therapeutic dosages, and cultures checked for sensitivity to itraconazole.

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Reprints: George J. Murakawa, MD, PhD, Division of Dermatology, MC-7, Albany Medical College, 47 New Scotland Ave, Albany, NY 12208 (e-mail: murakag@mail.amc.edu).

REFERENCES