MEDICAL INTELLIGENCE

INVASIVE ASPERGILLOSIS

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There is an increasing frequency of mycotic infections in patients with leukemia and other hematologic neoplasia.1-3 Aspergillosis is second only to candidiasis in frequency of opportunistic fungal disease among such patients.4-6 Invasive aspergillosis is difficult to diagnose and is often lethal in the immunosuppressed host.5,7 Blood cultures3,8 and serologic tests9 are usually negative with systemic disease. Skin lesions are infrequently reported in large series of patients with invasive aspergillosis3,7,10-12; however, we have observed cutaneous involvement in four patients during the past two years. The purpose of this paper is to describe the characteristic morphology of the skin lesions in these patients, and to suggest that the skin was the primary portal of the invading organism.

CASE REPORTS

Case 1. Idiopathic aplastic anemia developed in a 12-month-old boy. Three months later an irritant dermatitis was noted a few centimeters distal to the popliteal fossa, directly over the point of contact with a paper-covered board used to immobilize the leg for intravenous treatment; the board was in contact with the leg for seven days. A few days later, a 3-mm erythematous papule developed in the area of dermatitis. During the next two months, the lesion slowly progressed to a 6-cm ulcer with a central necrotic eschar (Fig. 1). Superficial scrapings from the lesion yielded negative bacterial and fungal cultures. X-ray study of the chest at that time was within normal limits. At the age of 17 months, x-ray examination showed a lytic lesion in the tibia underlying the ulcer. A biopsy revealed hyphae compatible with aspergillus in sections from both skin and underlying bone; the organisms were invading blood vessels in multiple areas. Cultures from skin and bone grew only *Aspergillus flavus*. A serologic test for aspergillus was negative on three different occasions while the disease was active.

At 17 months of age osteolytic lesions were noted in the skull, humerus and ribs. A rib biopsy revealed yeast and pseudohyphae compatible with candida, and cultures grew *Candida albicans*. Amphotericin B was started. The patient died one month later. Autopsy revealed a necrotizing aspergillus pneumonia. An illiac crest osteolytic lesion and muscle overlying the left tibia grew *A. flavus*. *A. fumigatus* was grown from the left-knee fluid. Necrotic foci of *C. albicans* were present in the liver and spleen. Bone marrow from the left humerus grew *C. tropicalis*. Blood cultures were negative for aspergillus. The cause of death appeared to be overwhelming fungal infection.

Case 2. Acute leukemia developed in a one-year-old girl. A remission was induced with vincristine and prednisone; she remained in remission for 13 months but then relapsed. During remission reinduction a poorly demarcated, slightly elevated 1-cm erythematous to violaceous patch developed on the right calf beneath a paper-covered board which immobilized the leg for an intravenous-infusion set; the board was in place for five days. During the next week the lesion became indurated and enlarged; the morphologic appearance changed to a deep violaceous plaque that progressed to a black necrotic central ulcer with a violaceous rim. A potassium hydroxide preparation from the lesion revealed organisms compatible with aspergillus. Culture grew *A. flavus*. A skin biopsy showed aspergillus hyphae invading vessels in the reticular dermis (Fig. 2). Amphotericin B was started. During the next week a similar lesion developed on the left calf, again adjacent to a...
paper-covered board securing an intravenous-infusion set; this board was in place for 3½ days. Though initial x-ray films were interpreted as normal, subsequent films during the terminal course revealed a progressive pneumonitis with pleural effusions. Numerous blood cultures were negative. The aspergillus serologic reaction was negative on two occasions during the active infection. The patient died three weeks after the initial ulcer was noted.

At autopsy, *A. flavus* was grown from the skin lesions and urine. Hyphae compatible with aspergillus were seen on tissue sections from the liver, spleen, heart, lungs, and kidneys. The cause of death was overwhelming aspergillus infection.

**Case 3.** Acute myelogenous leukemia developed in a 40-year-old male chicken farmer. During the hospital course, a 1-cm indurated erythematous nodule with a central pustule was noted on the left arm. The lesion did not appear to develop near an intravenous-infusion set. A skin biopsy revealed numerous hyphae consistent with aspergillus, and cultures from the biopsy grew *A. flavus*. X-ray study of the chest was normal. Oral 5-fluorocytosine and topical nystatin were added to amphotericin B therapy. The lesion progressed in five days to a painful 2-cm necrotic ulcer with an erythematous rim (Fig. 3). Biopsy showed dermal and subcutaneous fat necrosis associated with aspergillus invasion of the vessels.

Two months later, visual loss in the right eye developed. Ophthalmologic examination revealed a pale, well circumscribed lesion near the macula considered to represent an aspergillus endophthalmitis. Vision returned to normal, and the lesion resolved without specific antifungal therapy. The patient died nine months after the onset of the aspergillus infection in complete bone-marrow relapse with sepsis and acute renal failure.

Blood, sputum and urine cultures were negative for aspergillus, and there was no clinical or radiographic evidence of aspergillosis pneumonia. Aspergillus serologic reaction was not obtained. Permission for autopsy was denied, so that the presence or absence of a systemic aspergillus infection could not be substantiated.

**Case 4.** In this five-year-old boy idiopathic aplastic anemia developed at the age of three years. Ten weeks before death, a poorly demarcated erythematous papule was noted under adhesive tape on the proximal phalanx of the left index finger (day 0). This adhesive tape was securing the tubing of an intravenous-infusion set and was in place for 14 days. X-ray films of the chest at that time were normal. On day 3 a small central vesicle developed in the papule and ulcerated. Surface cultures and smears were negative. By day 5 the lesion had progressed to a central 5-mm necrotic eschar surrounded by a 2-cm erythematous and edematous base. Skin biopsy showed numerous hyphae invading blood vessels, and culture from the biopsy grew *A. flavus*. Intravenous amphotericin B therapy was started. The ulcer rapidly enlarged despite the addition of topical amphotericin B and oral 5-fluorocytosine. On day 11 there was a 1.5-cm central area of necrosis surrounded by a 2.5-cm erythematous, indurated and painful base (Fig. 4). The infection was too deep for simple surgical debridement and the finger and adjacent metacarpal head were amputated.

The patient died 44 days after the aspergillus skin lesion appeared. There was no definite evidence of pulmonary aspergillosis, but x-ray films of the chest showed infiltrates near the time of death. Blood cultures were negative, as was a serologic test for aspergillus. We could not confirm the suspected diagnosis of disseminated aspergillosis since permission for autopsy was denied.
Invasive *A. flavus* infections developed in four patients receiving immunosuppressive therapy for hematologic diseases. The skin manifestations were characterized by an erythematous to violaceous, edematous, indurated plaque that progressed to a necrotic ulcer with a central black eschar. Three patients had solitary lesions; one had two sites involved. The calf was infected in two cases, and the finger and arm were involved in one each. Four of the five skin lesions developed at the point of contact with adhesive tape or paper-covered boards that were securing intravenous-infusion sets; the paper or tape had been in place for 3½ to 14 days when the skin lesion was first noted. It may be possible to reduce these infections if intravenous sites are changed regularly or if the taping is periodically changed. Biopsy of the lesions in all four patients showed aspergillus invading blood vessels. The skin biopsies grew pure cultures of *A. flavus* in all cases. Blood cultures were always negative for aspergillus. Serologic studies* were obtained on three of the four patients, and were repeatedly negative. Cases 1 and 2 died with disseminated aspergillosis documented at autopsy; Case 4 may have died from disseminated aspergillosis, but permission for autopsy was denied, and Case 3 had endophthalmitis thought to be due to aspergillosis but had no other evidence of systemic involvement. The patients died from one to nine months after the lesions developed.

Cases of primary cutaneous and subcutaneous aspergillosis without clinically notable systemic involvement have been reported.12-20 Many of these patients were in apparent good health without an associated medical illness.14,16-19 *A. fumigatus* was isolated in three cases, and *A. niger* and *A. terreus* in two cases; *A. candidus* and *A. tamarii* were cultured in one patient each. Aspergillus infections may also complicate burn wounds and cause extensive local tissue destruction.

There are also several reports of cutaneous aspergillosis infections associated with systemic involvement. Findlay et al.11 group the skin lesions in these cases into five categories: the solitary necrotizing dermal plaque; the subcutaneous granuloma or abscess; persistent eruptive dermal maculopapules with suppurrative, vegetating or necrobiotic tendencies; miscellaneous erythemas and toxicodermas; and progressive confluent granulomas. Most of the patients with cutaneous aspergillosis with systemic involvement had multiple scattered lesions suggesting an embolic hematogenous spread from a primary pulmonary focus.3,11,22-26 *A. fumigatus* has been the most frequent species isolated in these cases. There has been one reported case of *A. flavus* causing a necrotizing ulcer with systemic involvement.3 The history and cutaneous morphology of this case are similar to those in our four patients: in a five-year-old child with acute lymphocytic leukemia, erythematous indurated cellulitis developed in the area of an intravenous needle. The solitary lesion rapidly progressed to a 2-cm ulcer with a black crust. Pneumonia followed in six days; the patient died nine days after the skin lesion appeared.3

It is of interest that in three of our four patients, the skin lesions developed at the point of contact with paper-covered boards or adhesive tape that were securing intravenous-infusion sets. This observation suggests the possibility of direct cutaneous inoculation as the source for disseminated infection with *A. flavus*, rather than the usual pulmonary portal. Pulmonary involvement is usually present in invasive aspergillosis, but was not detected before the skin manifestations in our patients. *A. fumigatus* is the most common cause of disseminated aspergillosis with cutaneous involvement.3,5,11

The cutaneous morphology of invasive aspergillosis is not distinctive enough to make a clinical diagnosis. The differential diagnosis includes other infectious causes of dermal necrotizing plaques that occur in immunosuppressed patients with hematologic disease.

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*All serum specimens were analyzed by the method of immunodiffusion performed at the Center for Disease Control, Atlanta, GA.*
Pseudomonas echyma gangrenosum is similar in appearance and is probably the most frequent cause of such lesions.\textsuperscript{22-31} Other differential diagnoses include mucormycosis,\textsuperscript{32,33} cryptococcosis,\textsuperscript{34-35} \textit{Aeromonas hydrophila} sepsis,\textsuperscript{36} phaeohyphomycosis (Estes SA, Merz WG, Maxwell LB: unpublished data), vasculitis\textsuperscript{37} and pyoderma gangrenosum.\textsuperscript{38} Invasive candidiasis usually manifests a disseminated erythematous nodular eruption rather than a solitary necrotizing plaque.\textsuperscript{39,40} Clearly, skin biopsy and culture are necessary for a definitive diagnosis.

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