JAMA Dermatology Clinicopathological Challenge

Gray-Violet Plaque in an Immunocompromised Girl

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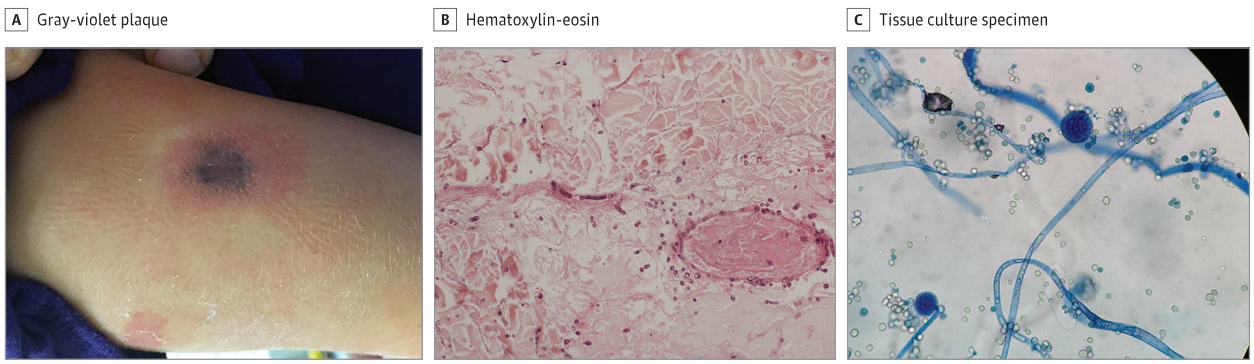

Figure. A, Gray-violet plaque on posterior upper arm at site of adhesive portion of bandage. B, Broad nonseptate hyphae surrounding and infiltrating dermal blood vessels (hematoxylin-eosin; original magnification ×400). Of note, occasional septae are seen in this specimen, consistent with the characteristic finding that mucormycetes are pauciseptate, rather than aseptate, molds. C, Nonseptate hyphae with round terminal sporangia and free spores (lactophenol cotton blue mount; original magnification ×400).

A 4-year-old girl with newly diagnosed acute lymphocytic leukemia, receiving her initial course of chemotherapy with vincristine, daunorubicin, and methotrexate, developed a painful lesion on her left triceps. The tender area was beneath an adhesive bandage placed where she had received DTaP (diphtheria-tetanus-pertussis) and polio vaccinations 3 weeks earlier. Otherwise, she appeared remarkably well, and her vital signs were normal. Removing the bandage revealed a tender indurated gray-violet plaque (**Figure**, A). White blood cell and neutrophil counts were low at 0.4 K/μL (normal range, 4.86-13.18 K/μL) and 0.18 K/μL (normal range, 1.60-8.29 K/μL), respectively. Blood culture findings were negative. Punch biopsy specimens were obtained for histopathologic analysis (Figure, B) and fungal culture (Figure, C).

WHAT IS YOUR DIAGNOSIS?

A. Mucormycosis

B. Cutaneous diphtheria

C. Pseudomonal ecthyma gangrenosum

D. Aspergillosis

Diagnosis

A. Mucormycosis

Microscopic Findings and Clinical Course

Histopathologic examination showed prominent broad nonseptated hyphae in the superficial and deep dermis surrounding and infiltrating several blood vessels, along with overlying areas of focal vacuolar interface changes at the dermal-epidermal junction (Figure, B). Microscopic examination of organisms grown from tissue culture revealed wide nonseptate hyphae with irregular branching, round terminal sporangia, and free spores (Figure, C). The histopathologic and tissue culture findings were consistent with a diagnosis of mucormycosis. The cutaneous lesion was completely excised. Treatment with intravenous liposomal amphotericin B was initiated. Her skin findings did not recur.

Discussion

Mucormycosis refers to an infection caused by fungi in the order Mucorales, which contain the genera *Mucor, Absidia*, and *Rhizopus*. These fungi are ubiquitous in the environment and are opportunistic pathogens that often cause fatal infections. A retrospective study[1] in children showed that mucormycosis was most commonly associated with hematologic malignancy (46%), followed by hematopoietic stem cell transplant (16%), other malignancies (7%), and solid organ transplant, trauma or surgery, and diabetes mellitus (5% each). Neutropenia was present in 46% of patients. Approximately one-third of these cases ended fatally. Risk factors in adults are similar and include immunocompromised states and history of trauma. Members of *Mucor* and related genera have been previously noted to cause cutaneous infections in susceptible patients at the attachment site of adhesive bandages and dressings, catheters, and drains.[2,3] Nosocomial outbreaks have also been linked to contaminated materials, such as hospital bed sheets, tongue depressors, and ostomy bags. A presumptive diagnosis of mucormycosis can be made when the histopathologic examination shows broad, largely nonseptate hyphae. The diagnosis is confirmed by microscopic examination of cultured material that shows wide (6-15 µm), largely nonseptate hyphae with irregular branching at 90° and long sporangiophores with round, spore-filled, terminal sporangia.

Aspergillosis, notably with *Aspergillus fumigatis* and *Aspergillus niger*, has also been reported at the site of adhesive bandages and tape in immunosuppressed patients.[4,5] On histopathological examination, aspergillosis appears as smaller, septate hyphae with regular 45° branching. Infection control guidelines have been proposed for tape storage and use but have not been widely implemented.[6]

Aggressive cutaneous bacterial infections are on the differential diagnosis for cutaneous plaques in immunosuppressed patients. Pseudomonal ecthyma gangrenosum is a necrotizing infection resulting from sepsis and subsequent angioinvasion by the gram-negative rod *Pseudomonas aeruginosa*. *Pseudomonas* invades the skin via hematogenous dissemination, not by percutaneous inoculation. Patients almost invariably show signs of sepsis.

Cutaneous diphtheria can cause ulceronecrotic plaques, surmounted by an adherent grayish membrane. It is transmitted by direct cutaneous inoculation of *Corynebacterium diphtheriae* via contaminated objects into the skin, usually in tropical climates.[7] It is not caused by diphtheria vaccination, which uses diphtheria toxoid (the toxin produced by *C diphtheriae*), not the organisms themselves.

Early diagnosis and treatment of cutaneous mucormycosis is vitally important. These fungi often invade endothelial cells and disseminate hematogenously, leading to poor outcomes.[8] Mucormycosis is resistant to many commonly used antifungal medications. Liposomal amphotericin B is the first-line treatment for mucormycoses,[2,8,9] at a recommended minimum daily dose of 5 mg/kg and in combination with surgical excision.[9] Prompt excision is particularly important in cases of percutaneous inoculation. Posaconazole is considered second line therapy. Isavuconazole shows little in vitro activity against Mucorales but shows promise in the clinical setting.[8] Voriconazole, which can treat aspergillosis, is not effective against mucormycoses and may enhance the virulence of *Rhizopus oryzae*.[10]

A high index of suspicion is necessary for rapid diagnosis and intervention in fungal infections in immunocompromised patients. Suspicious skin lesions should be biopsied immediately for histopathological examination and tissue culture. A fungal wet-prep or prompt frozen processing of the biopsy specimen may expedite diagnosis. Proper antimicrobial therapy and debridement or excisional surgery should be initiated as soon as possible to increase the chances of survival.

ARTICLE INFORMATION

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