Widespread Cutaneous Involvement by Invasive *Apophysomyces elegans* in a Gravid Patient Following Trauma

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Invasive infections in humans with organisms from the fungal subclass Zygomycetes are most commonly seen in immunocompromised and diabetic patients. Rarely, such fungal infections may be seen in immunocompetent, nondiabetic individuals. In these cases, cutaneous trauma with direct implantation of fungal organisms into the wound from soil contamination is the frequent scenario. We present the case of a 31-year-old gravid woman involved in a single-vehicle automobile accident who presented to our institution with severe head trauma. On admission, a small ecchymotic area on her right forearm was noted. The lesion eventually expanded and ulcerated. Culture and histologic examination of tissue from the site revealed fungal organisms consistent with Zygomycetes. Subsequent studies confirmed the fungal organism as Apophysomyces elegans. *Antifungal therapy was initiated, and multiple debridements were performed. Amputation of the right arm above the elbow was eventually necessary, but aggressive surgical intervention and antifungal therapy were unsuccessful in preventing the spread of the infection. The patient died 2 weeks after admission from polymicrobial sepsis. This case illustrates the dangerously invasive nature of* A elegans*, even in immunocompetent individuals.*

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Organisms of the class Zygomycetes, order Mucorales, family Mucoraceae/Absidiaceae, are pauciseptate mycelial fungi that cause significant infections in humans and include the genera *Absidia*, *Apophysomyces*, *Mucor*, *Rhizomucor*, and *Rhizopus*.[1] The organism most commonly isolated from human infections is *Rhizopus* species.[2] In tissue specimens, the Zygomycetes produce wide, ribbonlike hyphae with wide-angle branching and may elicit a predominantly neutrophilic inflammatory response, a predominantly granulomatous response, a mixed pyogranulomatous response, or no inflammatory response.[3] Although human zygomycotic infections are relatively uncommon compared with other fungal infections with organisms such as *Aspergillus* species and *Candida* species,[4] much higher rates of infection are seen in patients who are immunocompromised, immunosuppressed, diabetic, undergoing iron chelation therapy, or using broad-spectrum antibiotics or patients who have integumentary disruptions such as burns, trauma, and surgical wounds.[5-7] Zygomycetes are found in the environment in soil and on decaying plant material[8] and are transmitted to humans by the inhalation or ingestion of zygomycotic spores or by the contamination of wounds with spores.[9] Manifestations of infection include rhinocerebral, pulmonary, cutaneous, and gastrointestinal disease.[10] Zygomycotic infections show a notorious predilection for vascular invasion, producing infarcts and widespread necrosis in affected tissues.

Case Report

A 31-year-old pregnant woman was involved in a single-vehicle automobile accident. She was ejected from the vehicle after it struck a telephone pole and suffered extensive head injuries. The patient was transported to our facility by ambulance. On arrival, she was found to have near transection of her thoracic aorta, liver lacerations, small intestinal rupture, and lacerations on her upper extremities and face. After surgical repair of her injuries, the patient was transferred to the surgical intensive care

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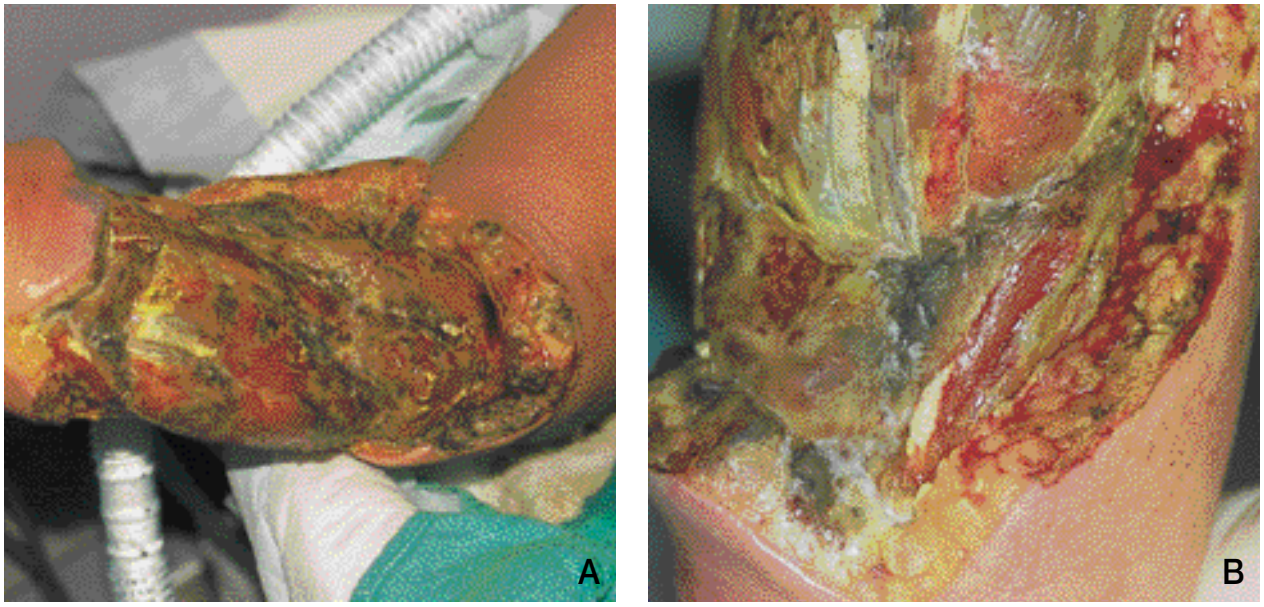

Figure 1. Right arm following multiple, extensive debridement procedures (A). Myonecrosis and grossly visible fungal organisms (white material in tissue crevices)(B).

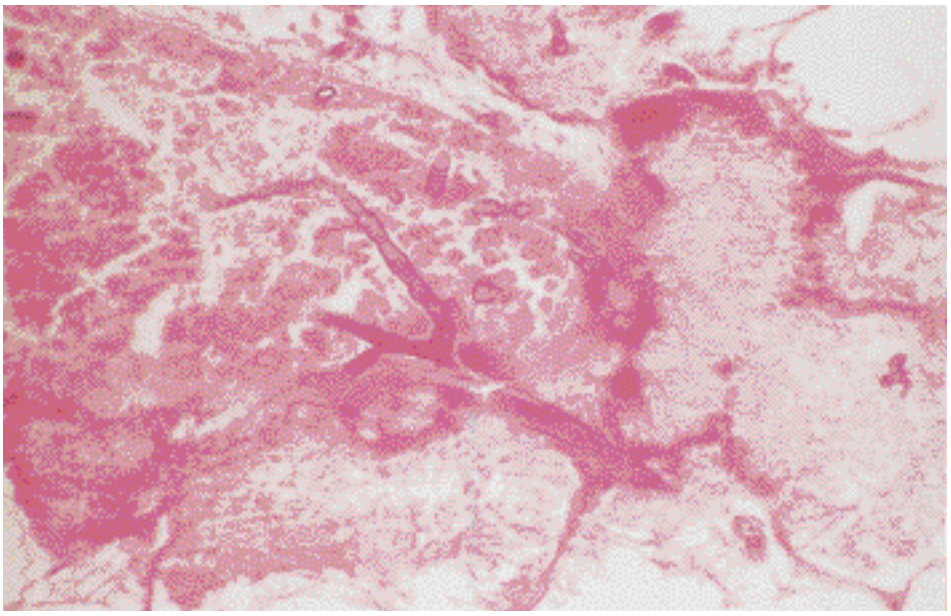

Figure 2. Broad pauciseptate hyphae of *Apophysomyces elegans* (H&E, original magnification ×40).

unit where she was given ventilatory assistance. Empiric antimicrobial coverage with cefazolin sodium was begun. The next day, vaginal bleeding was noted and the patient developed a fever of 101.5°F. The patient subsequently passed purulent-appearing material from the vagina, and a dilation and curettage procedure was performed. Histologic examination of the material showed findings compatible with a septic abortion. Gentamicin and clindamycin were added to the patient's antibiotic regimen. The patient remained febrile, and blood and urine cultures showed *Staphylococcus aureus* and *Candida albicans*, respectively. Renal failure developed, and dialysis was begun.

Over the next several days, an ecchymotic area was noted on the patient's right forearm that progressively enlarged to 5×4 cm and eventually ulcerated. Debridement of the area was performed, and the debridement tissue was submitted for culture and histologic analysis. A culture of the forearm lesion revealed *Serratia marsescens* and rare mold. Histologically, cellulitis and necrosis were

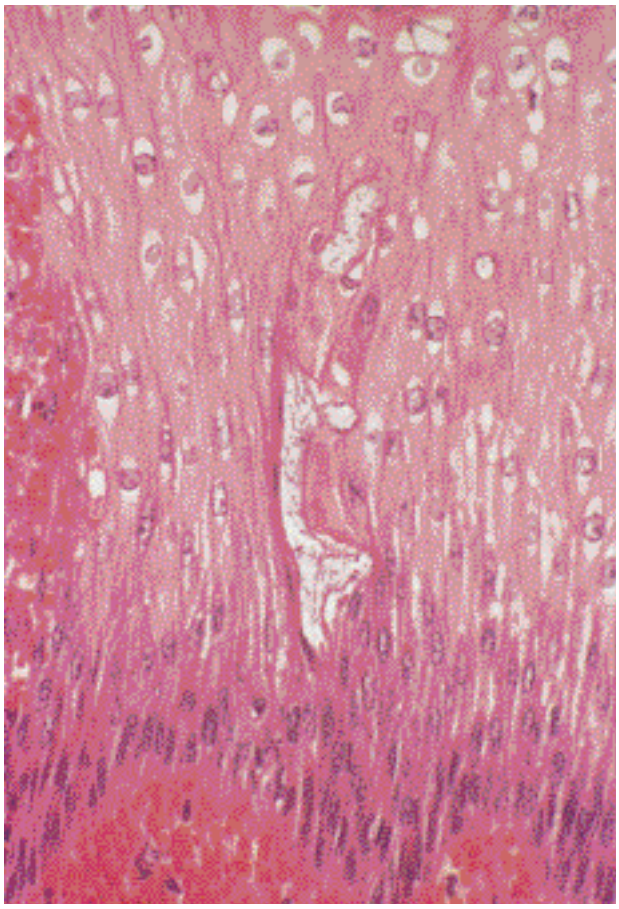

Figure 3. Fungal hyphae in the epidermis (H&E, original magnification ×40).

seen, as well as fungal organisms compatible with Zygomycetes. Sputum cultures taken at that time revealed *Acinetobacter baumannii* and *Enterobacter cloacae*. The patient's antibiotic regimen was changed to vancomycin, aztreonam, levofloxacin, metronidazole, and liposomal amphotericin B. The patient's forearm lesion continued to require daily debridement, and white aerial mycelia could be seen rising up to 1 cm above the surface of the wound. Subsequent wound cultures also showed fungal organisms consistent with Zygomycetes. Due to the severity of tissue necrosis of her forearm (Figure 1), the patient underwent an above-the-elbow amputation of the right arm. At the time of the right arm amputation, a biopsy of a 0.5×0.4-cm hyperemic area on the left hand was performed; fungal organisms consistent with Zygomycetes were identified in the biopsy. One week later, a necrotic lesion appeared on the patient's scalp. A 15×10-cm portion of scalp was removed; again, zygomycotic organisms were identified in the tissue. The patient continued to worsen clinically and died 2 weeks after admission. Significant gross findings at autopsy included enlarged pale kidneys and pulmonary edema.

Histologic examination of the debridement tissue from the right arm and the right arm amputation specimen showed pauciseptate fungal hyphae with wide-angle branching compatible with Zygomycetes (Figures 2 and 3). Extensive necrosis of skin, soft tissue, and muscle was present. Angioinvasion by Zygomycetes was seen in multiple sections (Figure 4), as well as prominent nerve invasion (Figure 5). In areas, vessels were occluded by fungal hyphae (Figure 6) and large areas of associated infarction with necrosis extended into the adjacent muscle and soft tissue. In most areas, an intense, predominantly neutrophilic inflammatory response was present, but in other areas, no inflammatory response was seen. The biopsy specimen from the left hand showed ulceration of the skin with dermal necrosis; fungal hyphae consistent with Zygomycetes were seen in the necrotic tissue. An intense, neutrophilic inflammatory response and necrosis in association with Zygomycetes also was seen in the resected scalp tissue. Special stains, including periodic acid–Schiff and Gomori methenamine-silver, highlighted the fungal forms in the tissue from all sites. Tissue sections taken during autopsy showed no fungal organisms in any internal organ.

Comment

Infection with fungal organisms of the class Zygomycetes, order Mucorales, are relatively uncommon causes of disease, representing as few as 5% of all human fungal infections in high-risk patients.[11] Zygomycetes are particularly prevalent in conditions that produce neutropenia or neutrophil dysfunction such as ketoacidosis and immunosuppression associated with chemotherapy or transplantation.[12] The Zygomycetes are seen most often as opportunistic infections in immunocompromised and diabetic patients. Zygomycotic infections in immunocompetent patients are rare and are usually associated with breaks in the skin barrier, such as burns and surgical wounds.[13] As in the current case, traumatic wound contamination with soil containing Zygomycetes has been reported as a rare source of infection.[14] Rare cases of percutaneous transmission also have been associated with needle sticks,[15] indwelling catheters,[16] insect bites,[17] and the use of adhesive tapes.[18]

Prompt diagnosis of zygomycotic infections is crucial due to the angioinvasive nature of the organisms and the possibility of widespread dissemination. Detection of zygomycosis involves a com-

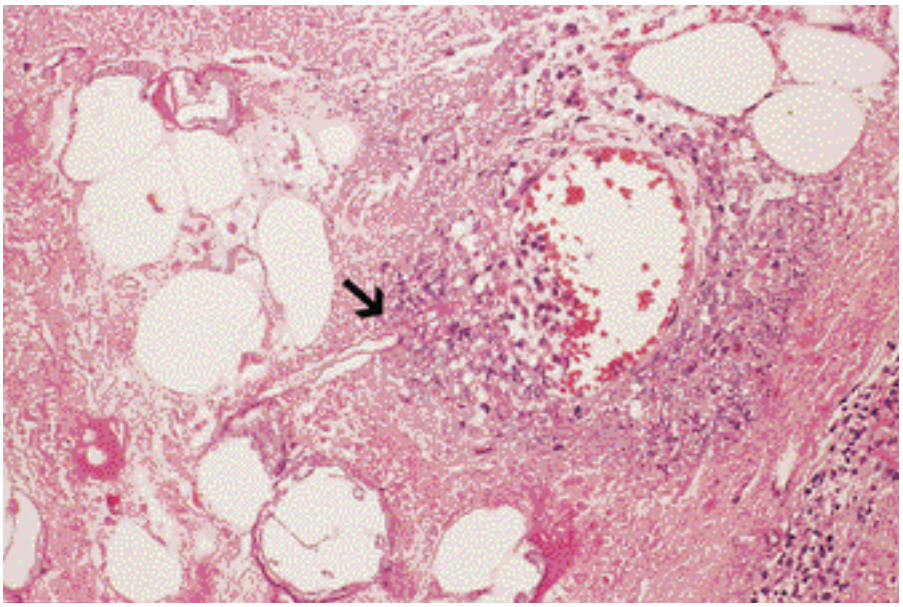

Figure 4. Vascular invasion by fungal hyphae (arrow) (H&E, original magnification ×20).

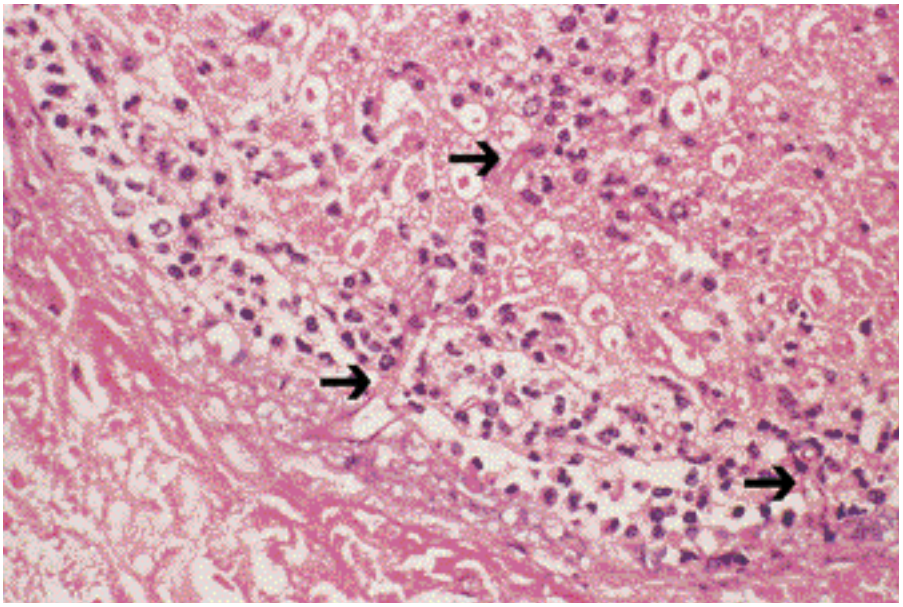

Figure 5. Nerve invasion by fungal hyphae (arrows)(H&E, original magnification ×40).

bination of diagnostic modalities including the identification of fungal hyphae in tissue sections combined with appropriate culture. In tissue sections, Zygomycetes appear as wide, ribbonlike, largely aseptate fungal hyphae that exhibit wide-angle (45°–90°) branching. The organisms show a marked angioinvasive tendency. In a recent series reported by Frater et al,[3] angioinvasion was seen in 100% of the 20 reviewed cases. Interestingly, in the same series, nerve invasion was seen in 90% of the reviewed cases that contained identifiable nerve tissue. Extensive nerve invasion also was identified in the current case. Although organisms of the class Zygomycetes, order Mucorales, are infamously invasive, most documented cases of neuroinvasion have been associated with central nervous system involvement in the rhinocerebral form of infection. Peripheral nerve involvement, however, has been described in the literature[3,19] and represents yet another pathway of dissemination for these aggressive organisms.

First described in 1979 by Misra et al,[20] *A elegans* is a soil-dwelling zygomycotic organism that primarily infects humans through contamination of cutaneous wounds with soil. Although primary cutaneous infection accounts for most cases of human disease, rare case reports have documented *A elegans* in a bronchial

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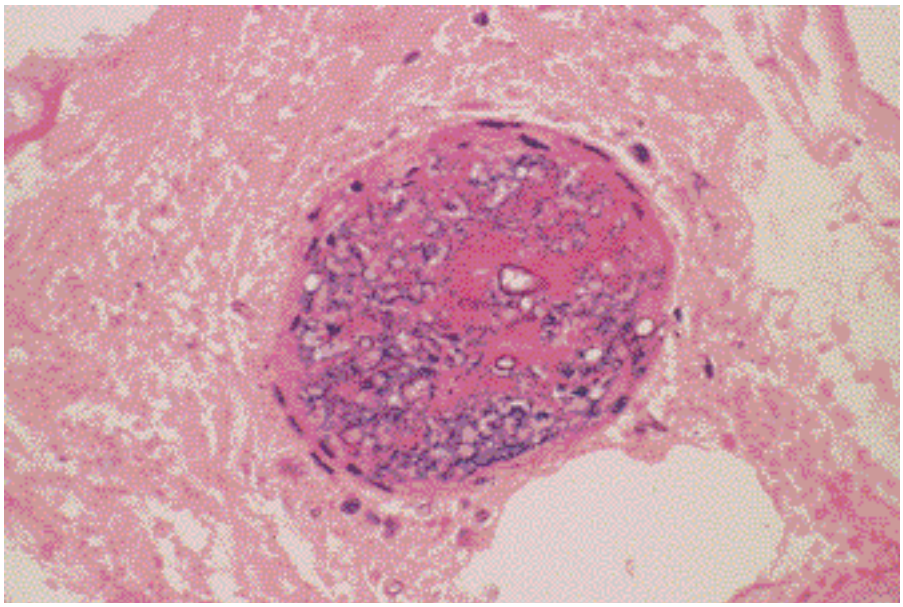

Figure 6. Fungal thrombus (H&E, original magnification ×40).

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washing[21] and as the cause of osteomyelitis.[22] Cases of renal and bladder involvement also have been documented.[22,23] Interestingly, most patients infected by *A elegans* show no evidence of immunocompromise prior to infection, a factor that may contribute to the lower death rate seen in *A elegans* infections compared with other zygomycotic infections. *A elegans* shows the same general morphology in tissue sections and predilection for vascular invasion as the other zygomycotic organisms; however, unlike some of the other Zygomycetes, *A elegans* fails to sporulate on standard culture media. Although a variety of culture methods have been attempted to precipitate sporulation and produce a more rapid identification of this organism, success has been variable. Exoantigen tests for the identification of strains of *A elegans* also have been developed.[25]

Successful treatment of zygomycosis requires aggressive antifungal therapy and surgical intervention. Cutaneous infections, such as in the current case, require debridement of infected wounds and possibly even amputation in combination with antifungal therapy. Amphotericin B is the antifungal agent of choice for zygomycotic infections; other antifungal agents such as itraconazole, nystatin, and fluconazole have proven ineffective in controlling the infection.[26] However, in circumstances such as those in the current case where compromised renal function is an issue, liposomal amphotericin B may be used with less risk of renal impairment. Although reported cases of zygomycosis have been treated successfully with antifungal therapy alone, these cases represented noninvasive infections; surgical intervention has been employed in the vast majority of successfully treated invasive fungal infections. The feasibility of surgical intervention, however, depends on the site of infection and the extent of invasion. Cases of respiratory infection that manifest as well-circumscribed fungus balls are usually amenable to surgical resection, as are cases of cutaneous infection confined to an extremity. Surgical procedures have much more limited value in cases of disseminated disease, consisting mainly of removal of devitalized tissue secondary to infarction caused by the fungal infection.

Bearing in mind that relatively few cases of *A elegans* infection have been reported, some authors have suggested that infections with *A elegans* show a lower mortality rate than other zygomycotic infections.[2] None the less, cutaneous infections with this organism may disseminate and be lethal. In the current case, the patient was pregnant at the time of her automobile accident, a condition that debatably may have produced immunosuppression. The patient's aborted placental tissue was reviewed microscopically and no fungal organisms were identified on routine sections or with special stains. During the course of treatment, the issue of dissemination of the patient's fungal infection was a matter of some uncertainty. With multiple skin abrasions as a result of her accident, the occurrence of cutaneous zygomycotic lesions at various sites could have represented primary infections from soil contamination or possibly disseminated disease from a single source. With the onset of renal failure

after her admission, the prospect of disseminated disease was of great clinical concern. At autopsy, however, routine sections and special stains showed no fungal organisms in any internal organ despite documented vascular invasion. Interestingly, no discernible skin damage was identified at any of the affected sites prior to the identification of infection. Although this is not surprising given the reports of *A elegans* infections following cutaneous insults as minor as insect bites and needle sticks, it also underscores the insidious nature of this rarely reported aggressive fungal organism.

REFERENCES

1. Chandler FW, Watts JC. Zygomycosis. In: Connor DH, Chandler FW, Schwartz DA, et al, eds. *Pathology of Infectious Disease*. Vol 2. Stanford, Conn: Appleton & Lange; 1997:1113-1119.
2. Ribes JA, Vanover-Sams CL, Baker DJ. Zygomycetes in human disease. *Clin Microbiol Rev*. 2000;13:236-301.
3. Frater JL, Hall GS, Procop GW. Histologic features of zygomycosis: emphasis on perineural invasion and fungal morphology. *Arch Pathol Lab Med*. 2001;125:375-378.
4. Roberts G. Labortory methods in basic mycology. In: Baron EJ, Finegold SM, eds. *Bailey & Scott's Diagnostic Microbiology*. 8th ed. St. Louis, Mo: CV Mosby Co; 1990:745-746.
5. Fisher J, Tuazon CU, Geelhoed GW. Mucormycosis in transplant patients. *Am Surg*. 1980;46:315-322.
6. Ryan-Poirier K, Eiseman RM, Beaty JH. Post-traumatic cutaneous mucormycosis in diabetes mellitus: short-term antifungal therapy. *Clin Pediatr*. 1988;27:609-612.
7. Mousa HA, Al-Bader SM, Hassan DA. Correlation between fungus isolated from burn wounds and burn care units. *Burns*. 1999;25:145-147.
8. Koneman EW, Allen SD, Janda WM, et al. Mycology. In: *Color Atlas and Textbook of Diagnostic Microbiology*. 5th ed. Philadelphia, Pa: Lippincott-Raven; 1997:999-1001.
9. Richardson MD, Koukila-Kähkölä P, Shankland GS. *Rhizopus, Rhizomucor, Absidia,* and other agents of systemic and subcutaneous zygomycoses. In: Murray PR, Baron EJ, Jorgenson JH, et al, eds. *Manual of Clinical Microbiology*. Vol 2. 8th ed. Washington, DC: ASM Press; 2003:1761.
10. Edwards JE, Pappas PG. Fungi and fungal diseases. In: Root RK, Waldvogel F, Corey L, et al, eds. *Clinical Infectious Disease: A Practical Approach*. New York, NY: Oxford University Press; 1999:46-47.
11. Gruhn JG, Sanson J. Mycotic infections in leukemic patients at autopsy. *Cancer*. 1963;16:61-72.
12. Brown AE. Overview of fungal infections in cancer patients. *Semin Oncol*. 1990;17:2-5.
13. Vainrub B, Macareno A, Mandel S, et al. Wound zygomycosis (mucormycosis) in otherwise healthy adults. *Am J Med*. 1988;84:546-548.
14. Adam RG, Hunter G, DiTomasso J, et al. Mucormycosis: emerging prominence of cutaneous infections. *Clin Infect Dis*. 1994;19:67-76.
15. Jain JK, Markowitz A, Khilanani PV. Case report: localized mucormycosis following intramuscular corticosteroid, case report and review of the literature. *Am J Med Sci*. 1978;275:209-216.
16. Oberle AD, Penn RL. Nosocomial invasive *Saksenae vasiformis* infection. *Am J Clin Pathol*. 1983;80:885-888.
17. Hicks WL, Nowels K, Troxel J. Primary cutaneous mucormycosis. *Am J Otolaryngol*. 1995;16:265-268.
18. Mead JH, Lupton GP, Dillavou CL, et al. Cutaneous *Rhizopus* infection: occurrence as a postoperative complication associated with an elasticized adhesive dressing. *JAMA*. 1979;242:272-274.
19. Newton WD, Cramer FS, Norwood SH. Necrotizing fasciitis from invasive phycomycetes. *Crit Care Med*. 1987;15:331-332.
20. Misra PC, Srivastava KJ, Lata K. *Apophysomyces*, a new genus of the *Mucorales*. *Mycotaxon*. 1979;8:377-382.
21. Ellis JJ, Ajello L. An unusual source for *Apophysomyces elegans* and a method for sporulation of *Saksenaea vasiformis*. *Mycologia*. 1982;77:144-145.
22. Meis JF, Kullberg BJ, Pruszczynski M, et al. Severe osteomyelitis due to the zygomycete *Apophysomyces elegans*. *J Clin Microbiol*. 1994;32:3078-3081.
23. Lawrence RM, Snodgrass WT, Reichel GW, et al. Systemic zygomycosis caused by *Apophysomyces elegans*. *J Med Vet Mycol*. 1986;24:57-65.
24. Okhuysen PC, Rex JH, Kapusta M. Successful treatment of extensive posttraumatic soft-tissue and renal infections due to *Apophysomyces elegans*. *Clin Infect Dis*. 1994;19:329-331.
25. Lombardi G, Padhye AA, Standard PG, et al. Exoantigen tests for the rapid and specific identification of *Apophysomyces elegans* and *Saksenaea vasiformis*. *J Med Vet Mycol*. 1989;27:113-120.
26. Caceres AM, Sardina C, Marcano R, et al. *Apophysomyces elegans* limb infection with a favorable outcome: case report and review. *Clin Infect Dis*. 1997;25:331-332.