A 56-YEAR-OLD MAN WITH ACUTE MYELOGENOUS LEUKEMIA DEVELOPS A VI-
laceous plaque on his anterior neck that expands rapidly over the course
of one day. The patient was hospitalized a month earlier for salvage che-
motherapy with clofarabine. His course has been complicated by prolonged neu-
tropenia and fever of unknown origin, for which he is receiving meropenem,
vancocmycin, and voriconazole. Physical examination reveals a necrotic-
appearing, nonblanching, violaceous plaque on his anterior neck with surround-
ing erythema (FIGURE 1). On close inspection, 2 similar violaceous papules are
discovered on his tongue and scalp. The patient is febrile but otherwise asym-
tomatic, with recent negative blood cultures.

Figure 1. Nonblanching and necrotic-appearing violaceous plaque on the patient’s anterior neck.

What Would You Do Next?
A. Draw repeat blood cultures
B. Order a computed tomography
scan of the head and neck
C. Perform a skin biopsy for frozen
section processing
D. Perform a skin biopsy for routine
permanent section processing

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Diagnosis
Disseminated angioinvasive fungal infection

What to Do Next
C. Perform a skin biopsy for frozen section processing

The key feature of this patient's physical examination is the nonblanching, violaceous, necrotic appearance of the plaque on his neck, which suggests vascular compromise in the dermis and devitalization of the underlying tissue. Given the rapidity of onset and the clinical history of prolonged febrile neutropenia, this lesion is worrisome for invasive infection and constitutes a medical emergency. Immediate diagnosis is required to guide management and reduce mortality.1

Comment
Angioinvasive fungal infection is a devastating complication of neutropenia, hematologic malignancy, or other profound or prolonged immunosuppression. Responsible organisms include those of the genera Aspergillus, Fusarium, Scedosporium, Mucor, and Rhizopus. Primary cutaneous infection may rarely occur following inoculation injury, such as at the site of an intravenous cannula. Other cutaneous lesions may result from direct extension of underlying infection or via hematogenous dissemination from the lungs or sinuses, in which case more than one lesion may be present.

The importance of a thorough physical examination should be emphasized. Lesions may be hidden under arm boards or tape, at intravenous line sites, or in anatomic areas not readily seen, including the genitals, mucosa, and scalp. Discovery of more than one lesion, as in this case, suggests dissemination, a distinction that changes management and prognosis. A complete skin examination is thus a vital part of the workup of any patient with neutropenia and fever. Skin lesions of angioinvasive fungal infection are typically violaceous papules or plaques with a tendency toward central necrosis resembling a “bull’s-eye infarct.”2 The differential diagnosis of such lesions includes other infectious or noninfectious processes that lead to vascular compromise and skin necrosis, such as erythema gangrenosum due to pseudomonal bacteremia, vasculitis, or vasculopathy.

Prompt diagnosis is essential to proper management. Histopathology showing tissue invasion by hyphae is definitive evidence of infection. If available, frozen section processing is preferred because results can be viewed in as little as 20 minutes. Permanent section processing yields higher-quality images and is a reasonable alternative, provided results can be obtained in a timely fashion. “Rush” specimens can be processed in as few as 6 hours but may take as long as 3 days depending on when the specimen is submitted. Institutional variability exists with respect to pathology services, particularly after hours; frozen section processing is widely available, and most hospitals have on-call pathology staff to support the technique.

Isolated primary cutaneous lesions should be treated aggressively. Surgical debridement of a solitary lesion affords the best chance of cure. Systemic antifungal therapy should be initiated but alone is often insufficient; secondary dissemination may occur if the lesion is not excised. If multiple lesions are present or there is evidence of disseminated disease, systemic antifungals should be administered, but mortality approaches 100% without immunologic recovery. Adjuvant measures such as activated granulocyte infusions and granulocyte colony-stimulating factor may be used in some cases, despite little evidence of benefit.3

Voriconazole is the agent of choice for invasive aspergillosis and is also effective against Fusarium and Scedosporium. Because aspergillosis is the most common cause of angioinvasive fungal infection, voriconazole is frequently used as prophylactic or empirical therapy in neutropenic patients. However, Rhizopus, Mucor, and other zygomycetes are resistant to voriconazole and are typically treated with amphotericin B. Some have suggested that widespread use of voriconazole prophylaxis in susceptible patients may be a risk factor for developing zygomycosis.4,5

Patient Outcome
In this patient, a biopsy of the neck lesion was submitted for immediate processing by frozen tissue pathology. Numerous thick, ribbon-like, translucent, nonseptate hyphae filled the lumen of a subcuticular vessel with destruction of the vessel wall and invasion of the dermis, findings consistent with angioinvasive fungal infection (Figure 2). Computed tomography of the chest and abdomen revealed new pulmonary infiltrates and renal infarcts. Despite immediate initiation of amphotericin B for probable zygomycosis, the patient died 48 hours later following hemorrhage of an undetected frontal lobe lesion, presumably a focus of disseminated fungal infection.

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REFERENCES

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