Case 22-2009: A 59-Year-Old Man with Skin and Pulmonary Lesions after Chemotherapy for Leukemia

Thomas F. Patterson, M.D., Bonnie T. Mackool, M.D., Matthew D. Gilman, M.D., and Adriano Piris, M.D.

Dr. Deborah L. Cummins (Dermatology): A 59-year-old man was seen by consultants in infectious disease and dermatology because of cutaneous and pulmonary lesions that developed after induction chemotherapy for acute myeloid leukemia.

A diagnosis of myelodysplastic syndrome had been made 13 months earlier at another hospital. Since that time, the patient had been hospitalized repeatedly elsewhere for pancytopenia and had received transfusions of red cells and platelets. (The results of laboratory tests obtained 12 weeks before admission to this hospital are shown in Table 1.) Six weeks before admission to this hospital, the patient received azacitidine subcutaneously, followed 15 days later by pegfilgrastim. Nine days before this admission, the patient presented to the outpatient cancer center of this hospital with chills and fever of 2 to 3 days’ duration. The temperature was 38.9°C; the remainder of the examination was normal. He was admitted to this hospital. Electrolyte levels and tests of renal function were normal; the results of other laboratory tests obtained on this admission are shown in Table 1. Analysis of the urine revealed 1+ albumin. Specimens of blood and urine were obtained for culture, and cefepime, vancomycin, and prednisone were administered. Filtered red cells (4 units) and platelets were transfused. Pathological examination of a biopsy specimen of the bone marrow disclosed the presence of acute myeloid leukemia. The blood cultures remained sterile. The patient was discharged on the fourth hospital day; his medications included levofloxacin, prednisone, and omeprazole daily. Six days later, he was readmitted to the hospital for induction chemotherapy.

A diagnosis of hepatitis C virus infection had been made approximately 20 years earlier. A 48-week course of treatment with ribavirin and interferon had been initiated 27 months earlier. Ten weeks before admission, a plasma sample showed no detectable hepatitis C viral ribonucleic acid.

The patient had been depressed, a condition thought to be related to interferon therapy. He was single and had worked in the construction industry before retirement. He had traveled to the Southwest 30 years earlier but had never traveled internationally. He smoked cigarettes for 30 years, had a history of alcohol abuse decades earlier but reported no recent use, and did not use illicit drugs. His father had died.
of a brain abscess at the age of 41 years, and his mother had died of congestive heart failure at the age of 75 years.

On examination, the temperature was 36.5°C, the blood pressure 118/70 mm Hg, the pulse 77 beats per minute, and the respiratory rate 18 breaths per minute, with 98% oxygen saturation while the patient was breathing ambient air. Physical examination showed petechiae in the oropharynx, gingival bleeding, and several cutaneous ecchymoses; the remainder of the examination was normal. Tests of renal and liver function and levels of protein, albumin, and globulin were normal; the results of other laboratory tests obtained on the second hospital admission are shown in Table 1.

A triple-lumen intravenous catheter was placed in the right internal jugular vein, and a 3-day course of idarubicin and a 7-day continuous infusion of cytarabine were begun. Transfusions of filtered red cells and platelets were given as needed. White plaques developed on the tongue, which were consistent with thrush, and fluconazole was added to the regimen. On the seventh hospital day, neutropenia, nausea, and diarrhea developed, followed by abdominal pain and fever, with a temperature as high as 38.4°C. Specimens of blood and urine were obtained for culture and remained sterile. The stool was negative for ova, parasites, bacterial pathogens, and Clostridium difficile toxin. Treatment with vancomycin, cefepime, and metronidazole was begun intravenously. On the 10th day, computed tomography (CT) of the abdomen showed evidence of acute appendicitis. Total parenteral nutrition was begun. CT of the pelvis performed 2 days later showed thickening of the sigmoid and descending colon, which was consistent with colitis; an unchanged appearance of the appendix, with no evidence of perforation; and multiple prominent retroperitoneal lymph nodes, up to 1.1 cm in diameter. The abdominal pain gradually resolved, and oral intake was resumed 1 week later. A red, raised rash developed on the upper arms and groin, and nystatin powder was administered.

On the 15th hospital day, a biopsy specimen of bone marrow revealed residual leukemia. Laboratory-test results are shown in Table 1. The next day, petechiae were noted on the shins and knees. On the 17th day, a second course of chemotherapy with cytarabine and idarubicin was begun. During the next week, nonpruritic, red, raised lesions developed on the chest and arms. The patient reported severe pain (rated 10 on a scale of 1 to 10, with 10 being the most severe) in both heels; the heels were erythematous and were tender on palpation. Heel protectors were provided. Blood cultures remained sterile. Treatment with vancomycin and fluconazole was continued; levofloxacin, cefepime, and metronidazole were withdrawn, and famciclovir and meropenem were added. On the 27th day, a hemorrhagic blister developed on the left heel. Diarrhea recurred; a test for C. difficile toxin was negative, and treatment with metronidazole was resumed. On the 29th day, the temperature rose to 38.4°C. Pathological examination of a biopsy specimen of the bone marrow showed hypocellular marrow with no evidence of leukemia. Treatment with filgrastim was begun.

On the 31st day, the temperature rose to 38.6°C. CT of the chest showed bilateral pulmonary nodules, 2 to 4 mm in diameter. CT of the abdomen showed resolution of both the appendiceal changes and the colonic-wall thickening. On examination, the blood pressure was 110/60 mm Hg, the pulse 112 beats per minute, the respiratory rate 22 breaths per minute, and the oxygen saturation 97% while the patient was breathing ambient air. Crackles were heard in both lung bases, and there was 3+ edema of the legs. Numerous erythematous, firm cutaneous nodules, 1 to 4 cm in diameter, were present on the abdomen, chest, head, upper arms, and legs. There were scattered petechiae on the legs and trunk. On the right foot, erythema of the fourth toe and a papule on the third metatarsal were noted; there was a necrotic plaque, 2 cm in diameter, on the left heel. There was no lymphadenopathy, and the remainder of the examination was normal. Specimens of blood and urine were cultured. Tests of serum for galactomannan and 1,3-β-D-glucan were negative. Other test results are shown in Table 1. Metronidazole and fluconazole were discontinued, and amphotericin B and atovaquone were added.

On the 32nd hospital day, a diagnostic procedure was performed.

**Differential Diagnosis**

Dr. Thomas F. Patterson: Pulmonary and cutaneous nodules developed in this 59-year-old man 31 days after he received induction chemotherapy for acute myeloid leukemia. Because the spectrum of causative agents associated with infections in a patient...
such as this one is broad, it is imperative to establish a diagnosis in order to guide therapy. Early and effective therapy, combined with successful management of the underlying malignant tumor and reversal of immune defects, is critical for a favorable outcome. This patient was appropriately treated with antifungal therapy (liposomal amphotericin B), pending the results of an extensive evaluation that included cultures of blood and urine and nonculture-based tests for fungi (galactomannan and 1,3-β-D-glucan), which remained negative. Chest and abdominal radiography are important in the diagnosis of opportunistic infection in patients with severe immunosuppression. May we review the imaging studies?

Dr. Matthew D. Gilman: CT scans of the abdomen (on the 10th hospital day) and pelvis (on the 12th day), obtained after the administration of intravenous and oral contrast material, showed an enlarged, thickened appendix with mucosal hyperenhancement and periappendiceal fat stranding, with no evidence of perforation (Fig. 1A). A diagnosis of appendicitis was made. Abdominal CT scans obtained on the 31st hospital day showed resolution of the appendicitis. CT scans of the chest showed bilateral, well-defined pulmonary nodules, 2 to 4 mm in diameter (Fig. 1B and 1C), which had not been present on chest CT scans obtained 4 weeks earlier. There was neither lymphadenopathy nor pleural effusion.

### Table 1. Laboratory Data.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Reference Range, Adults*</th>
<th>12 Wk before Admission</th>
<th>First Admission</th>
<th>Second Admission</th>
<th>15th Hospital Day</th>
<th>31st Hospital Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematocrit (%)</td>
<td>41.0–53.0 (men)</td>
<td>21.7</td>
<td>24.3</td>
<td>29.3</td>
<td>30.2</td>
<td>25.3</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>13.5–17.5 (men)</td>
<td>8.6</td>
<td>10.2</td>
<td>10.7</td>
<td>9.5</td>
<td></td>
</tr>
<tr>
<td>White-cell count (per mm³)</td>
<td>4,500–11,000</td>
<td>2200</td>
<td>3,700</td>
<td>2900</td>
<td>400</td>
<td>200</td>
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<td>Differential count (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophils</td>
<td>40–70</td>
<td>35</td>
<td>9</td>
<td>7</td>
<td>8</td>
<td>0</td>
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<td>Band forms</td>
<td>0–10</td>
<td>2</td>
<td>2</td>
<td>1</td>
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<tr>
<td>Lymphocytes</td>
<td>22–44</td>
<td>53</td>
<td>64</td>
<td>75</td>
<td>84</td>
<td>100</td>
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<td>Monocytes</td>
<td>4–11</td>
<td>3</td>
<td>6</td>
<td>3</td>
<td>4</td>
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<td>Atypical lymphocytes</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>4</td>
<td>0</td>
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<td>Metamyelocytes</td>
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<td>1</td>
<td>1</td>
<td>5</td>
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<td>0</td>
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<tr>
<td>Blasts</td>
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<td>2</td>
<td>16</td>
<td>8</td>
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<tr>
<td>Total white cells counted</td>
<td></td>
<td>25</td>
<td></td>
<td></td>
<td>15</td>
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<tr>
<td>Nucleated red cells (per 100 white cells)</td>
<td>150,000–350,000</td>
<td>32</td>
<td>26</td>
<td>24</td>
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<td>Platelet count (per mm³)</td>
<td></td>
<td>7000</td>
<td>12,000</td>
<td>7000</td>
<td>31,000</td>
<td>10,000</td>
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<td>Activated partial-thromboplastin time (sec)</td>
<td>22.1–34.0</td>
<td>27.9</td>
<td>28.2</td>
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<td>Prothrombin time (sec)</td>
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<td>10.3–13.2</td>
<td>13.8</td>
<td>13.5</td>
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<td>International normalized ratio</td>
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<td>1.2</td>
<td>1.5</td>
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<td>Fibrinogen (mg/dl)</td>
<td></td>
<td>150–400</td>
<td>548</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilirubin (mg/dl)†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>0.0–1.0</td>
<td>2.0</td>
<td>1.7</td>
<td>0.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Direct</td>
<td>0.0–0.4</td>
<td>0.6</td>
<td>0.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lactic dehydrogenase (U/liter)</td>
<td>110–210</td>
<td>1245</td>
<td>837</td>
<td>190</td>
<td>140</td>
<td></td>
</tr>
</tbody>
</table>

* Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges used at Massachusetts General Hospital are for adults who are not pregnant and do not have medical conditions that could affect the results. They may therefore not be appropriate for all patients.

† To convert the values for bilirubin to micromoles per liter, multiply by 17.1.
Dr. Patterson: The differential diagnosis of pulmonary nodules associated with cutaneous lesions is broad for this patient who received induction chemotherapy for acute myeloid leukemia (Table 2). Although noninfectious explanations, such as leukemic infiltrates or skin lesions of Sweet’s syndrome, are possible in severely immunosuppressed patients such as this one, infectious causes should be the primary consideration because of the need for prompt initiation of therapy.

**Bacterial Infections**

The development of a resistant bacterial infection is an important consideration in this patient. *Pseudomonas aeruginosa* produces the necrotic skin lesions of ecthyma gangrenosum, which are associated with hematogenous spread of infection. Other gram-negative bacteria, such as *Stenotrophomonas maltophilia*, aeromonas, and a host of Enterobacteriaceae, can produce similar findings. Methicillin-resistant *Staphylococcus aureus*, contracted in community and health care facilities, is another important concern, and clostridium species and viridans streptococci should also be considered. But in this patient, infection with these typical bacterial pathogens seems unlikely, since cultures of blood and urine remained negative.

*Mycobacterium tuberculosis*, as well as atypical mycobacteria, such as *M. marinum*, which cause distinctive skin lesions, could be considered in this patient. Nocardia species can cause extensive pulmonary infection, although the infection is usually cavitary in nature and disseminated infection can produce widespread cutaneous lesions. In this patient, there was no suggestion of exposure or a history that would lead to the diagnosis of mycobacterial disease or nocardiosis.

An additional concern in this patient was the development of acute abdominal pain and the finding of colitis on radiographic imaging after his initial course of induction chemotherapy. The development of neutropenic enterocolitis or typhilitis occurs most commonly after intensive chemotherapy. Although bacterial pathogens, most frequently gram-negative organisms from the gut, are typically associated with this complication, the negative blood cultures in this patient raise the possibility of other pathogens. Recent series have shown that fungal enterocolitis may cause 5% of typhilitis cases. *Candida* species account for more than 90% of these cases, although other mycoses, including aspergillus, fusarium, zygomycetes, cryptococcus, and trichosporon, have been reported. Fungal enterocolitis is rare, but it should be considered, given the difficulty...
of diagnosing it and the high mortality associated with its occurrence. However, blood cultures remained negative while this patient was receiving broad-spectrum antibiotics and fluconazole, and his abdominal symptoms and radiographic abnormalities diminished.

**INVASIVE FUNGAL INFECTIONS**

The risk of opportunistic infection in immunocompromised patients with hematologic cancer can be estimated by determining the net state of immunosuppression. The interaction of a number of factors is taken into account. They include the dose, sequence, and intensity of chemotherapy; the duration and severity of neutropenia; the extent to which the mucocutaneous barrier is compromised by mucositis or indwelling catheters; malnutrition or other preexisting illnesses; infection with immunomodulating viruses, especially cytomegalovirus; and age. Specific risk factors for invasive mycoses have been described in patients with hematologic cancers; persistent neutropenia (more than 13 months in duration) combined with refractory leukemia requiring a second course of chemotherapy puts this patient at substantially increased risk for an invasive fungal infection, which should be a focus of his diagnostic evaluation and treatment.

The incidence of invasive fungal infection and associated mortality remains high, despite advances in diagnosis and therapy. Candida remains a clinically significant pathogen, even though fluconazole prophylaxis has reduced the incidence of candida infection. Skin lesions associated with disseminated infection are relatively common and may be an important clue to this diagnosis. Lesions are usually macronodular and are either single or multiple, occurring over the entire body, although lesions resembling ecchyma gangrenosum or purpura fulminans have been described. Pulmonary disease is not common, although candida pneumonia has been reported in patients with hematologic cancers. Because this patient was receiving fluconazole, the most likely candida species would be those resistant to fluconazole, such as *Candida krusei* or *C. glabrata*. Although blood cultures lack sensitivity, the administration of antifungal therapy,

### Table 2. Clinical and Mycologic Characteristics of the Most Common Invasive Molds in Hematologic Cancers.

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Clinical Characteristics</th>
<th>Mycologic Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspergillus species</td>
<td>Most common invasive mold; appears most frequently as invasive pulmonary aspergillosis; disseminated infection, including skin in about 20% of patients; primary skin inoculation (necrotic lesion) in about 5% of patients</td>
<td>Blood cultures often not positive; non–culture-based methods (tests for galactomannan and 1,3-β-D-glucan) may facilitate diagnosis; polyene resistance in some species (e.g., <em>A. terreus</em>); preferred therapy is with voriconazole</td>
</tr>
<tr>
<td>Fusarium species</td>
<td>Disseminated infection with pulmonary nodules and characteristic erythematous, nodular skin lesions, which may have a necrotic center; initial portal of entry often onychomycosis or nail lesion</td>
<td>Blood cultures positive in up to 50% of cases; clinical and microbiologic resistance to polyenes common; better susceptibility to voriconazole and posaconazole; poor outcomes without reversal of underlying immune defect or cancer</td>
</tr>
<tr>
<td>Zygomycetes</td>
<td>Sinus and pulmonary involvement common; primary skin lesion more common than skin lesions resulting from hematologic dissemination; associated with use of voriconazole as immunosuppressive therapy</td>
<td>Characteristic ribbonlike appearance, with rare appearance of cross-walls on histopathological examination; cultures of homogenized tissues may be negative; preferred therapy is with high-dose liposomal amphotericin B or posaconazole</td>
</tr>
<tr>
<td>Scedosporium species</td>
<td><em>S. apiospermum</em> common in respiratory tract, brain abscesses, and skin nodules; associated with near-drowning; <em>S. prolificans</em> associated with disseminated infection in patients with severe immunosuppression</td>
<td><em>S. apiospermum</em> resistant to polyenes, more susceptible to extended treatment with broad-spectrum azoles; <em>S. prolificans</em> is dematiaceous; multiantifungal drug resistance; blood cultures positive in about 50% of patients</td>
</tr>
<tr>
<td>Phaeohyphomycosis (bipolaris, exophiala, wangiella, and others)</td>
<td>Associated with disseminated and central nervous system infection in immunosuppressed patients; pulmonary, sinus, and cutaneous lesions from dissemination or primary infection</td>
<td>Melanin-containing hyphae seen with use of specific stains (e.g., Masson–Fontana) on histopathological examination; irregular hyphal shape; fungemia may be present in some species (e.g., exophiala); preferred therapy is with newer azoles or polyene</td>
</tr>
</tbody>
</table>
the absence of positive cultures, and the atypical clinical presentation reduce the likelihood of infection with candida species in this patient.

Other yeasts can also contribute to this type of clinical presentation. Cryptococcus is reported in patients with hematologic cancers but is more common in allograft recipients, who have impaired T-cell function. Pulmonary and disseminated disease occurs, but the skin lesions typically appear as pedunculated, dome-shaped papules with an umbilicated center, in contrast to those described in this patient. One third of patients who are infected with trichosporon species present with pneumonia and disseminated disease in association with erythematous papules, which may become necrotic. Trichosporon shares cross-reactive antigenicity with cryptococcus that results in a positive cryptococcal antigen test, as would be expected in cases of disseminated infection with either of these two pathogens.

Although uncommon, infection with endemic mycoses is also an important consideration in immunosuppressed patients, including those with hematologic cancers. Disease occurs either as a result of new infection after an environmental exposure or as a result of reactivation of a remote infection. Patients with cellular immunodeficiencies appear to be at the greatest risk and can be susceptible to severe pulmonary infection and widespread disseminated infection. We know that our patient traveled to the Southwest many years ago but have no other specific epidemiologic information that would suggest an endemic fungal infection.

Molds, particularly aspergillus, pose the greatest risk of invasive fungal infection in patients undergoing intensive chemotherapy for hematologic cancers (Table 2). Although an understanding of the risk factors for invasive aspergillosis continues to evolve, profound and prolonged neutropenia remains a major risk factor. Pulmonary infection is the most common clinical presentation; primary cutaneous infection occurs in approximately 5% of patients infected with aspergillus, and disseminated infection occurs in approximately 20% of such patients. Radiographic evaluation early on can be an important adjunct to the diagnosis, since nodular lung disease (usually in the form of macronodules with or without a surrounding halo of low attenuation) is present in more than 90% of patients with invasive pulmonary aspergillosis. The skin lesions associated with primary infection with aspergillus are typically more localized and necrotic than those observed in this patient. Generalized skin lesions, such as those seen in this patient, are not common in disseminated aspergillosis, although they have a variety of clinical presentations. Blood cultures are not positive, and single samples obtained for nonculture-based testing (galactomannan and 1,3-β-D-glucan) may be falsely negative. Aspergillosis must be a serious consideration in this patient, and empirical antifungal therapy should include coverage of this organism.

Zygomycetes have also emerged as important pathogens in patients with severe immunosuppression. Skin lesions from disseminated zygomycosis are uncommon but are typically necrotic in appearance when they do occur. Our patient is at risk for zygomycosis because of his hematologic cancer; however, he does not have other common risk factors, which include prior prophylaxis with voriconazole or echinocandin, diabetes, malnutrition, sinusitis, iron overload, or prior chemotherapy with deoxyxamine.

Finally, the incidence of infection with fusarium species has increased substantially in patients with hematologic cancers and in those undergoing stem-cell transplantation. Fusarium is a common organism found in water and biofilms and can also colonize skin. Risk factors for infection include severe and prolonged neutropenia as well as disruption of skin integrity through infection or trauma. Onychomycosis has been described as an important predisposing condition. This patient is described as having necrotic lesions on his heel, which could have been a portal of entry for this organism. Skin lesions of disseminated fusariosis are typically nodular and deeply erythematous, as described in this patient. Although there is substantial overlap in the clinical manifestations of invasive mycoses, the appearance of this patient’s skin lesions strongly suggests the likelihood of infection with fusarium. A biopsy of these lesions should be performed to establish a diagnosis. Blood cultures can be an important clue, and one would expect that eventually blood cultures would be positive for the organism, as they are in at least 50% of patients. The mortality associated with disseminated fusarium infection approaches 100% among patients who do not recover from their underlying neutropenia or cancer.
APPROACH TO DIAGNOSIS AND INITIAL THERAPY

Establishing a diagnosis of mycologic infection can be difficult. Cultures of blood are useful for yeasts but are of more limited value for molds. Serologic assays in immunosuppressed patients may be falsely negative. The usefulness of nonculture-based methods is limited: tests for the presence of galactomannan in blood are relatively specific for aspergillus but have low sensitivity, especially in the absence of serial testing and in patients receiving mold-active therapy. The test for 1,3-β-D-glucan is nonspecifically positive for a variety of organisms, including aspergillus and fusarium, but not for zygomycetes and possibly not for cryptococcus. Negative test results for these organisms do not rule out fungal infection. In a patient with skin lesions, a biopsy specimen that is assessed with appropriate cultures and stains is most likely to yield a diagnosis.

In summary, invasive fungal infection appears to be the likely cause of this patient’s pulmonary and cutaneous nodules. The widespread erythematous cutaneous nodules associated with the necrotic lesions on his heel suggest that fusarium is the likely pathogen.

Dr. Eric S. Rosenberg (Infectious Disease and Pathology): Dr. Mackool, what was your clinical impression when you saw this patient?

Dr. Bonnie T. Mackool: At the time of the consultation, the patient had several erythematous, tender nodules on the trunk, arms, and legs (Fig. 2A). A few shiny and more deeply erythematous nodules were present on the wrist and foot (Fig. 2B). Petechiae were seen on the abdomen and arms and legs but were less numerous than they were a few days later. My colleagues and I thought that deep fungal infection was the most likely cause of the cutaneous lesions but we were also concerned about the possibility of bacterial infection. The presence of pulmonary lesions along with cutaneous findings heightened our suspicion of infection with fusarium. Disseminated yeast infection and aspergillosis were also considered. Lesions in fusarium infection are typically pain-

Figure 2. Skin Lesions.
The patient had petechiae, multiple erythematous, tender nodules on the trunk, arms, and legs (Panel A), as well as several nodules on his foot that were shiny and more deeply erythematous (Panel B).
Figure 3. Cutaneous Biopsy Specimen.
A low-power view of the deep dermis and subcutaneous fat shows focal chronic inflammation (Panel A, hematoxylin and eosin). Deep dermal vessels show chronic inflammation and extravasated erythrocytes as evidence of vessel-wall involvement (Panel B, hematoxylin and eosin). Periodic acid–Schiff staining with diastase highlights the presence of septate hyphae with acute angle branching (Panel C); a cluster of organisms is lodged in the vessel wall. Gomori’s methenamine silver stain shows marked vessel-wall involvement with fungal hyphae (Panel D).
ful, erythematous nodules and necrotic ecthyma gangrenosum–like lesions, with some target lesions showing necrosis and a rim of erythema. We also considered Sweet’s syndrome and leukemia cutis, but the characteristics of the skin lesions in combination with the presence of pulmonary nodules led us to consider fusarium infection as the most likely diagnosis.

**Clinical Diagnosis**

Disseminated fusariosis.

**Dr. Thomas F. Patterson’s Diagnosis**

Disseminated fusariosis.

**Pathological Discussion**

*Dr. Adriano Piris:* A skin biopsy of one of the abdominal lesions was performed. Routine microscopical examination showed an inflammatory process in the deep dermis and subcutaneous fat, with a vasculitic component (Fig. 3A and 3B). Periodic acid–Schiff staining with diastase and Gomori’s methenamine silver staining revealed abundant septate hyphae with acute angle branching involving deep dermal vessels and subcutaneous fat, findings that are consistent with invasive fungal infection (Fig. 3C and 3D). These fungal forms are morphologically consistent with aspergillus or fusarium species. The tissue culture was positive for *Fusarium solani* species complex, establishing the diagnosis of disseminated fusarium infection.

*Dr. Rosenberg:* Dr. Cummins, what happened to this patient?

*Dr. Cummins:* On the basis of the biopsy results, treatment with intravenous voriconazole was initiated on hospital day 35. Despite declining renal function, the patient also continued to receive liposomal amphotericin B. The patient continued to have high fevers, despite antifungal and antibiotic therapy. There seemed to be a modest improvement in some of the cutaneous nodules, and no new lesions developed, but most of the existing lesions on the chest, abdomen, and arms and legs persisted. On hospital day 41, CT of the chest showed enlargement of the pulmonary nodules. At this time, the patient also had noncardiogenic pulmonary edema, presumably related to the disseminated fungal infection and worsening renal function. A complete blood count revealed 20% blasts, indicating a relapse of the leukemia. The patient died on the 46th hospital day.

*Dr. Jay A. Fishman* (Medicine, Infectious Disease): Could you comment on the question of potential antagonism between the polyene class of antifungal agents and the azole antifungal agents, which has been controversial for some time? As was pointed out, this patient was treated with both a lipid formulation of amphotericin B and voriconazole.

*Dr. Patterson:* The possibility of antagonism between the polyenes and the azole class of drugs is a concern because the reduction in ergosterol at the cell membrane by the azoles effectively eliminates the site of action for the polyenes. There is no firm evidence of antagonism between these two classes of drugs in fusariosis, but preclinical studies suggest that echinocandins might act synergistically with the azoles against some molds. In this patient, the persistence of leukemia was a greater contributor to the poor outcome than was antagonism between the drugs.

**Anatomical Diagnosis**

Disseminated fusarium infection involving the lungs and skin.

Dr. Patterson reports receiving consulting fees from Basilea, Merck, and Pfizer, lecture fees from Merck and Pfizer, and grant support from Basilea, Nektar Therapeutics, Pfizer, and Schering-Plough for the University of Texas Health Science Center at San Antonio; he also reports serving as an expert witness in one case for the U.S. Department of Justice. No other potential conflict of interest relevant to this article was reported.

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**References**

5. Fishman JA. Infection in solid-organ...

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CORRECTION

Case 22-2009: A 59-Year-Old Man with Skin and Pulmonary Lesions after Bone Marrow Transplantation

Case 22-2009: A 59-Year-Old Man with Skin and Pulmonary Lesions after Bone Marrow Transplantation. The article title should have read, “Case 22-2009: A 59-Year-Old Man with Skin and Pulmonary Lesions after Chemotherapy for Leukemia.” The error appears on the cover of the July 16 issue, on page 287, and in the weekly CME. The article has been corrected at NEJM.org.