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Case Studies

A 53-Year-Old Male with Relapsed Diffuse Large B-Cell Lymphoma on Chemotherapy with a New Leg Lesion

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Abstract
Patients with underlying malignancy who develop new skin findings while acutely ill often require skin biopsy for histologic evaluation and/or culture to reach a diagnosis. Here, we present the case of a 53-year-old male with relapsed diffuse large B-cell lymphoma on chemotherapy who developed new skin lesions on the leg. On exam, there were 2 nickel-sized, erythematous to violaceous round plaques with central necrotic cores on the right lower leg with relatively nonspecific clinical features for which the initial differential diagnosis was broad. Consensus on a diagnosis was reached upon histologic evaluation of his skin biopsy in the context of his clinical setting. This diagnosis led to a change in treatment plan, with subsequent clinical improvement.

Case Report

A 53-year-old male with a history of relapsed diffuse large B-cell lymphoma presented with respiratory failure, altered mental status, and distributive shock 4 days status post cycle 1 of rituximab, ifosfamide, carboplatin, and etoposide (RICE) chemotherapy. History was notable for rhinorrhea and cough prior to presentation. Chest CT scan was notable for numerous nodular bilateral opacities concerning for pneumonia. Initial microbiology studies

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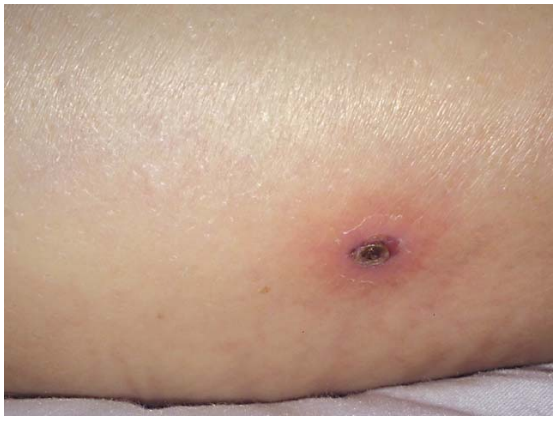

Fig. 1. Erythematous to violaceous plaque with central necrotic core and faint surrounding collarette of scale on the right lower leg. Photo: courtesy of Dr. Avery LaChance. A 3-mm punch biopsy was performed on the right leg.

were notable for a positive bronchoalveolar lavage for *Moraxella catarrhalis,* an elevated (1,3)-β-D-glucan of 184 pg/mL (reference range <60 pg/mL), and negative blood cultures for bacteria or fungi. The patient was treated empirically with vancomycin, cefepime, and azithromycin with little improvement. He remained intubated, requiring pressor support, intravenous fluids, and albumin despite these interventions. Four days after admission, the patient was noted to have developed new cutaneous lesions on the right lower leg. On examination, there were 2 round, red, firm nickel-sized plaques with a central violaceous, necrotic core and collarette of scale on the right lateral lower leg and right medial ankle (Fig. 1). Additionally, there was one red-grey macule on the left shin.

Diagnosis and Clinical Course

Histopathologic examination revealed invasive fungal infection with focal angioinvasion and thrombotic vasculopathy (Fig. 2). Grocott-Gomori methenamine silver nitrate, Fontana, and periodic acid-Schiff/diastase stains showed pigmented fungal hyphae within dermal tissue and focally within small vessels (Fig. 2). Fite, acid-fast bacilli, and Gram stains were negative, and *Aspergillus* immunostain was negative. Tissue culture was positive for *Alternaria* species. The histopathologic findings, in conjunction with the patient's immunosuppression, clinical history, and elevated fungal markers, were suggestive of disseminated *Alternaria* infection. Intravenous liposomal amphotericin B was initiated at 375 mg daily for 10 days. The patient was then transitioned to isavuconazole 372 mg daily and discharged with a plan for a 6-week course of treatment. Four weeks later, following return of final sensitivity data showing a favorable minimal inhibitory concentration of posaconazole, the patient was transitioned to lifetime posaconazole therapy.

Discussion

The term phaeohyphomycosis describes a fungal infection caused by a dematiaceous (brown-pigmented) fungus. Among the causative agents of phaeohyphomycosis is *Alternaria*, a genus encompassing nearly 300 species widely found in soil and air, as well as on plant surfaces and human skin [1]. Rarely pathogenic in immunocompetent hosts, an *Alternaria* infection in an immunosuppressed individual can cause cutaneous and subcutaneous infections, oculomycosis, onychomycosis, and sinusitis and, in severe cases, disseminated disease

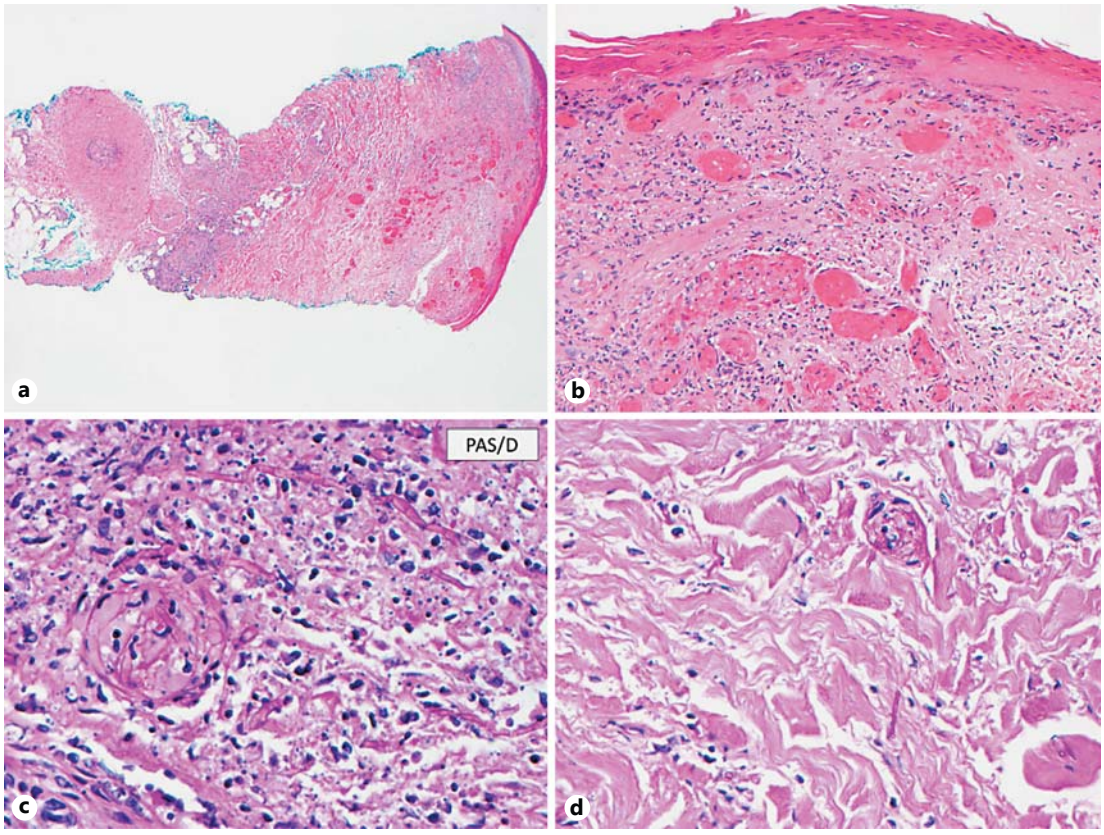

Fig. 2. Punch biopsy of the right lower leg. **a** Low-power view of HE. **b** Higher-power view of HE. **c** Periodic acid-Schiff/diastase (PAS/D) stain demonstrating fungal hyphae and "hand grenade in chains" appearance consistent with *Alternaria*. **d** PAS stain showing angioinvasion of the fungal hyphae into a small vessel.

involving multiple organ systems [1, 2]. Cutaneous infection typically occurs via direct inoculation through traumatic breaks in the skin [3]. Clinically, cutaneous lesions appear as solitary or multiple nodules and plaques, often with a verrucous or ulcerated appearance [3]. Histopathologic features associated with cutaneous phaeohyphomycosis include epidermal hyperplasia, inflammatory granulomas, and occasionally intraepidermal abscesses and ulceration [3–5]. Fungal hyphae forms may be visualized in the dermal tissue [4, 5].

Immunosuppressed patients are susceptible to localized and disseminated infections with phaeohyphomycoses from dematiaceous fungi, a collection of fungi that characteristically incorporate melanin in the cell wall. Due to the presence of melanin, the dematiaceous fungi appear histologically as brown-black-pigmented hyphae in culture and in tissue [6, 7]. Melanin is thought to be a key virulence factor allowing dematiaceous fungi to escape host defenses by scavenging free radicals and inhibiting phagocytosis [8].

The most common dematiaceous fungi implicated in phaeohyphomycosis are the *Alternaria* species [7]. While a majority of *Alternaria* cases have been reported in transplant recipients [2], individuals with Cushing disease [9], hematologic malignancy [10], and those who are immunosuppressed due to chemotherapy or corticosteroid treatment are also susceptible [3]. Rarely, cases of immunocompetent hosts presenting with alternariosis have been reported [11]. Phaeohyphomycoses are most commonly localized infections of the cutaneous and adjacent subcutaneous tissue. Clinically, these lesions appear as painless nodules and plaques, often with central ulceration [1]. The most common distribution for such cutaneous

lesions is on the extremities [7]. In severe cases, however, phaeohyphomycosis can become disseminated and present with systemic symptoms, such as fevers, as well as involvement of pulmonary, gastrointestinal, and/or central nervous systems [12].

Diagnosis of phaeohyphomycosis depends upon histologic and microbiologic confirmation. At present, there are no available serologic tests that reliably distinguish the dematiaceous fungi [6]. Antigen-based tests, such as (1,3)-β-D-glucan and galactomannan, are not consistently positive for causative agents of phaeohyphomycosis [13]. Early histologic changes associated with cutaneous phaeohyphomycosis include epidermal hyperplasia, inflammatory infiltrates, and microabscesses [4], followed by evolution of inflammatory, suppurative, and purulent granulomas [5]. With regard to special stains, the melanin-specific Masson-Fontana stain is highly sensitive, but not specific, for the identification of dematiaceous fungi in tissue [14]. Caution should be used when interpreting the Masson-Fontana stain due to cross-reactivity with nondematiaceous species, such as *Aspergillus* and some zygomycetes [14]. Additionally, fungal hyphae of dematiaceous species consistently stain positive with Grocott-Gomori methenamine silver nitrate and periodic acid-Schiff [5]. Fungal culture is needed to definitively identify the causative organism. Furthermore, *Alternaria* and other dematiaceous molds are common laboratory contaminants [15]; thus, it is critical that a positive fungal culture be not dismissed as a contaminant in cases with consistent clinical and histologic picture.

In our patient, systemic symptoms, lack of initial improvement on broad-spectrum antibacterial coverage, histopathologic findings revealing angioinvasion, as well as global improvement once on antifungal therapy were all suggestive of disseminated phaeohyphomycosis. Elevated (1,3)-β-D-glucan further supported a diagnosis of disseminated, rather than localized, phaeohyphomycosis, though it should be noted that there are reports of false-positive (1,3)-β-D-glucan in the setting of albumin and human blood product administration [16, 17].

Phaeohyphomycosis among individuals who are immunosuppressed is associated with significant mortality, especially if diagnosis is delayed or overlooked. Overall mortality of phaeohyphomycosis among transplant recipients at 1 institution over 20 years was reported at 19% [5], and mortality of disseminated phaeohyphomycosis has been reported as high as 79% [12]. Isolated cutaneous lesions may be surgically excised in addition to treatment with either an oral or intravenous antifungal [12]. The azoles (itraconazole, voriconazole, posaconazole, and the relatively newer agent isavuconazole) are generally effective options for phaeohyphomycosis, and combination therapy including amphotericin B with an azole may be considered for disseminated disease [12, 18]. Choice of therapy should be guided by antifungal susceptibility testing when available. This case highlights the intricacies of diagnosis and treatment of phaeohyphomycosis, specifically *Alternaria*, in an immunocompromised host. When working up a new lesion in an immunocompromised patient, one must have low threshold for biopsy to assess for infection and consider species that are not typically pathogenic, including *Alternaria*.

Statement of Ethics

The manuscript was prepared in compliance with all ethical and confidentiality guidelines and principles.

Disclosure Statement

The authors have no conflicts of interest to disclose.

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