Angioinvasive *Alternaria alternata* presenting with violaceous papules and plaques in the setting of chronic lymphocytic leukemia

Caitlyn Kellogg, MD,a Elise Burger, MD, PhD,b Brian R. Hinds, MD,b and Jeremy A. Schneider, MDb

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**INTRODUCTION**

Infection remains a leading cause of death in patients with chronic lymphocytic leukemia (CLL), as a result of immunodeficiencies attributable to the disease and its treatments. Immunocompromised hosts are at high-risk for acquiring serious opportunistic infections. Local skin and soft tissue infections are common, but skin lesions may be a critically emergent clue to disseminated disease.1

Cutaneous lesions of ecthyma gangrenosum (most commonly related to *Pseudomonal* bacteremia) result from bacterial invasion into—and subsequent damage/destruction of—blood vessel walls. *Pseudomonal* species are particularly adept at causing vascular injury related to production of exotoxin A, elastase, and phospholipase C2 though multiple other organisms can trigger various cataclysmic vascular injuries.3,4

We present a case of cutaneous angioinvasive *Alternaria alternata* masquerading as ecthyma gangrenosum in a CLL patient with known *Pseudomonas* bacteremia and invasive *Aspergillus* sinusitis.

**REPORT OF A CASE**

A 73-year-old woman with CLL on ibrutinib therapy presented to a local hospital with weakness and fatigue and was found to be pancytopenic with *Pseudomonas* bacteremia.

Upon transfer to our hospital, a non-tender and non-pruritic, solitary thin plaque was noticed on the patient’s left lateral shin, with violaceous perimeter and central black eschar (Fig 1).

The lesion appeared prior to transfer, in parallel with identification of *Pseudomonas* bacteremia. Given her *Pseudomonas* bacteremia and clinical appearance, the lesion was presumed to represent ecthyma gangrenosum and the patient was continued on meropenem. Biopsy was discussed for additional diagnostic delineation, but was initially deferred by the patient citing increased risks of bleeding/further infection risk. Labs on admission to our hospital included an absolute neutrophil count of 0 × 10⁹/L (normal range, 2.5-7 × 10⁹/L), hemoglobin of 8 g/dl (normal range, 12-16 g/dl for females), and platelet count of 39 × 10⁹/L (normal range, 150-400 × 10⁹/L).

One week after our initial evaluation, the patient developed 2 similar-appearing scaly red-purple papules with dusky borders on the right elbow (Fig 2) and right dorsal hand (Fig 3) while the shin lesion persisted. She was also diagnosed with acute sinusitis, but while blood cultures were no longer growing

From the School of Medicine, University of California San Diego, San Diego, California a; and Department of Dermatology, University of California San Diego, San Diego, California. b

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Correspondence to: Caitlyn Kellogg, MD, School of Medicine, University of California San Diego, 6501 Forum St, San Diego, CA 92111. E-mail: ckellogg@dhs.lacounty.gov.

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Pseudomonas, new bacteremia with vancomycin-resistant Enterococcus ensued. Given the presence of new lesions and the persistence of her shin lesion despite treatment for her Pseudomonas bacteremia, concern for an alternative etiology for the skin findings was redoubled, and, in this setting, the patient consented to punch biopsies of the shin lesion. Histopathologic examination was consistent with infectious fungal vasculopathy and staining with both Periodic acid-Schiff (PAS) and Grocott’s methenamine silver (GMS) revealed easily identifiable clusters of hyphal and spore forms, the former of which exhibited septations with acute-angle branching (Fig 4). Gram stain was negative for bacterial superinfection.

Shortly thereafter, she was diagnosed with invasive fungal sinusitis. Culture of the shin lesion grew A.alternata and she was initially diagnosed with A.alternata invasive fungal sinusitis with systemic dissemination; however, sinus biopsy revealed fungal hyphae to be morphologically consistent with Aspergillus.

The patient was started on amphotericin B and isavuconazonium, chosen based on combination of sensitivity data and interaction potential with her chemotherapy. She underwent multiple rounds of sinus debridement. At the time of discharge, her clinical status had improved and her neutropenia had reversed; however, her infection had not yet resolved, with recommendation to continue antimicrobial treatment and likely further outpatient sinus debridement.

DISCUSSION

This case highlights the dichotomy between the competing diagnostic forces of Occam’s razor, in which parsimony in diagnosis acts as a guiding principle (i.e., the simplest explanation or the explanation in which the fewest individual diagnoses can account for a patient’s signs/symptoms generally prevails over more complex explanations), versus Hickam’s dictum, which counters this argument, positing that a patient “can have as many diseases as [he or she] pleases.”5 Particularly when evaluating complex patients with multiple comorbidities, as in this case and in an immunocompromised host, it is important to consider the possibility of co-occurring diseases even when a single diagnostic entity may initially seem like an appropriate explanation.

Multiple infectious organisms can co-occur in severely immunocompromised patients, creating significant diagnostic difficulties. In this case, the patient had numerous causes of immunosuppression including CLL, ibrutinib, rituximab, and systemic corticosteroids. Typically, ibrutinib should be held in the setting of neutropenia and the dose should be modified after infection resolution6; in this case, however, it was initially continued until it was appropriate to transition the patient to venetoclax given concern for disease progression. Initially, the solitary shin lesion, which clinically appeared consistent with ecthyma gangrenosum, was attributed to the

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**Fig 1.** Solitary, violaceous 1.1 × 0.9 cm plaque with violaceous perimeter and central black eschar on the left lateral shin.

**Fig 2.** Thin dusky papule with violaceous rim and fine scale on the right elbow.

**Fig 3.** Thin scaly erythematous papule with violaceous rim on the right dorsal hand.
known *Pseudomonas* bacteremia. However, in the setting of progressive skin lesions while on meropenem, punch biopsy and tissue culture revealed cutaneous *A. alternata*. Furthermore, ethmoid sinus biopsy ultimately revealed a second documented fungal infection with *Aspergillus*.

Common infections involving the skin of an immunocompromised host include *Pseudomonas, Stenosphomomas, Nocardia, Mycobacteria, Candida, Cryptococcus, Aspergillus, Fusarium, Zygomycetes*, and *Phaeohyphomycosis* including *Alternaria*.\(^1\) Skin manifestations of these infections may have a nonspecific appearance, which is often overlooked or misidentified in early morphologic stages due to overlapping clinical features and a weakened immune response to the causative organism(s).\(^1\) This

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**Fig 4.** A 3 mm punch biopsy, left lateral shin. Hematoxylin and eosin (A) reveals a vasculopathic reaction with hemorrhage, and purpura. Periodic acid-Schiff stain (B) and Grocott's Methenamine Silver stain (C) reveal multifocal clusters of hyphal septated forms with variable, acute-angle branches and spores.
A perfect storm can lead to diagnostic ambiguity and delay, particularly if/when a patient has multiple comorbidities and infectious organisms.

Phaeohyphomycosis refers to infection caused by dematiaceous fungi, most commonly caused by A.alternata, an opportunistic fungus affecting immunocompromised patients. Other reports of cutaneous A.alternata have described variable clinical features, including macules, ulcers, and papules/plaques. Alternaria tends to present as a single cyst or plaque in immunocompetent patients and progresses to nodules, eschars or ulcers, which may disseminate to other organs in immunosuppressed patients.

Mycological features of A.alternata include macroconidia and thin walled hyphae with acute angle branching and septations. Azoles can effectively treat diffuse Alternaria skin infections, though antifungal susceptibility testing should be performed due to reports of itraconazole treatment failure.

Cutaneous manifestations may be difficult to differentiate in immunocompromised patients with multiple infections. Although a patient’s cutaneous lesion may fit clinically with his/her known infection and clinical presentation, diagnostic parsimony might be inconsistent, and providers should maintain high suspicion for additional culprit organisms and use reliable microbiology laboratories for tissue culture/identification.

Conflicts of interest
None disclosed.

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