Pink Ulcerated Nodule on the Forearm

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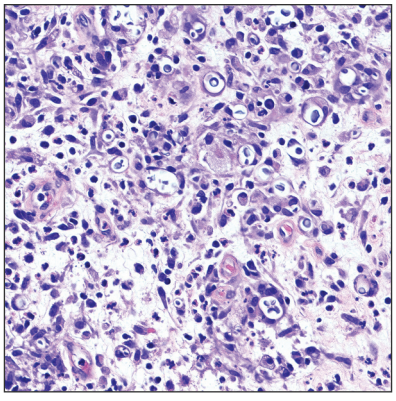
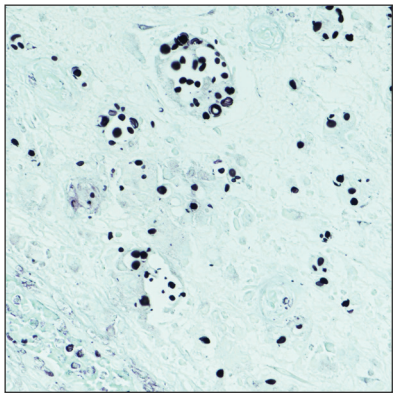


H&E, original magnification ×40.



Grocott methenamine silver, original magnification ×40.

A 51-year-old man with a history of multiple sclerosis treated with fingolimod presented to the dermatology department with an ulcerated lesion on the left forearm of 2 to 3 months' duration. The patient reported that he recently presented to the emergency department for drainage of the lesion, which was unsuccessful. Shortly after, he traumatized the lesion at his construction job. At the current presentation, physical examination revealed a 1-cm, flesh-colored to faintly pink, ulcerated nodule on the left forearm. A biopsy was performed.

THE BEST **DIAGNOSIS IS:**

a. cutaneous blastomycosis
b. cutaneous cryptococcosis
c. cutaneous histoplasmosis
d. foreign body granuloma
e. Sweet syndrome

PLEASE TURN TO PAGE 129 FOR THE DIAGNOSIS

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THE **DIAGNOSIS:** Cutaneous Cryptococcosis

Biopsy of the ulcerated nodule showed numerous yeastlike organisms within clear mucinous capsules and with some surrounding inflammation. On Grocott methenamine silver staining, the organisms stained black. Workup for disseminated cryptococcus was negative, leading to a diagnosis of primary cutaneous cryptococcosis in the setting of immunosuppression. Notably, cryptococcosis infection has been reported in patients taking fingolimod (a sphingosine-1-phosphate receptor) for multiple sclerosis, which was the case for our patient.[1]

The genus *Cryptococcus* comprises more than 30 species of encapsulated basidiomycetous fungi distributed ubiquitously in nature. Currently, only 2 species are known to cause infectious disease in humans: *Cryptococcus neoformans*, which affects both immunocompromised and immunocompetent patients and frequently is isolated from pigeon droppings, as well as *Cryptococcus gatti*, which primarily affects immunocompetent patients and is more commonly isolated from soil and decaying wood.[2]

Primary cutaneous cryptococcosis (PCC), characterized by direct inoculation of *C neoformans* or *C gatti* via skin injury, is rare and typically is seen in patients with decreased cell-mediated immunity, such as those on chronic corticosteroid therapy, solid-organ transplant recipients, and those with HIV.[3] Primary cutaneous cryptococcosis typically manifests as a solitary or confined lesion on exposed areas of the skin and often is accompanied by regional lymphadenopathy.[4,5] The most common cutaneous findings associated with PCC include ulceration, cellulitis, and whitlow.[5] In immunocompetent hosts, frequently affected sites include the arms, fingers, and face, while the trunk and lower extremities are more commonly affected in immunocompromised hosts.[3] Secondary cutaneous cryptococcosis occurs through hematologic spread in patients with disseminated cryptococcosis after inhalation of *Cryptococcosis* spores and differs from PCC in that it typically manifests as multiple lesions scattered on both exposed and covered areas of the skin. Patients also may have signs and symptoms of disseminated cryptococcosis such as pneumonia and/or meningitis at presentation.[5]

Despite the difference between PCC and secondary cutaneous cryptococcosis, almost every type of skin lesion has been observed in cryptococcosis, including pustules, nodules, vesicles, acneform lesions, purpura, ulcers, abscesses, molluscumlike lesions, granulomas, draining sinuses, and cellulitis.[6,7]

Cutaneous cryptococcosis generally is associated with 2 types of histologic reactions: gelatinous and granulomatous. The gelatinous reaction shows numerous yeastlike organisms ranging from 4 µm to 12 µm in diameter with large mucinous polysaccharide capsules and scant inflammation. Organisms may be seen in mucoid sheets.[8] The granulomatous type shows a more pronounced reaction with fewer organisms ranging from 2 µm to 4 µm in diameter found within giant cells, histiocytes, and lymphocytes.[6,9] Areas of necrosis occasionally can be observed.[8]

It is important to consider infection with *Blastomyces dermatitidis* and *Histoplasma capsulatum* in the differential diagnosis of cryptococcosis. Both entities can manifest as necrotizing granulomas on histology (Figures 1 and 2).[10] Microscopic morphology can help differentiate these pathogenic fungi from *Cryptococcus* species which show pleomorphic, narrow-based budding yeast with wide capsules. In contrast, *H capsulatum* is characterized by small, intracellular, yeastlike cells with microconidia and macroconidia, while *B dermatitidis* is distinguished by spherical, thick-walled cells with broad-based budding.[11] Capsular material also can

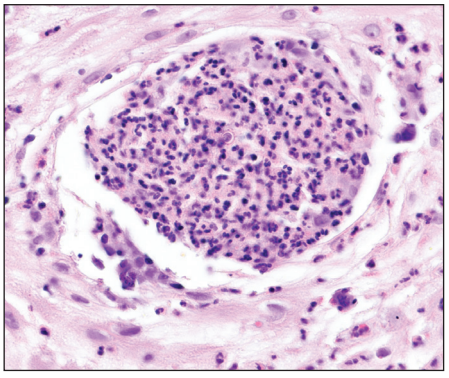

FIGURE 1. Cutaneous blastomycosis showing necrotizing granuloma with a spherical thick-walled organism centrally (H&E, original magnification ×40).

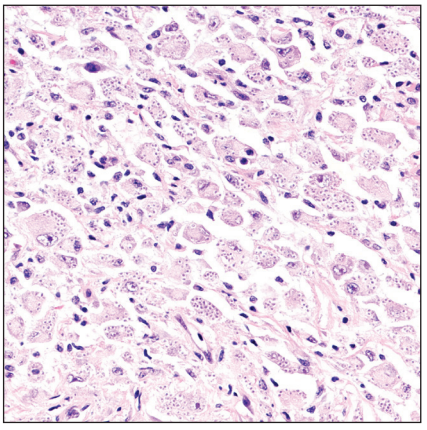

FIGURE 2. Cutaneous histoplasmosis showing numerous parasitized histiocytes with intracellular yeast forms (H&E, original magnification ×60).

help distinguish *Cryptococcus* from other pathogenic fungi. Special stains highlighting the polysaccharide capsule of *Cryptococcus* can best identify the yeast. The capsule stains red with periodic acid–Schiff, blue with Alcian blue, and black with Grocott methenamine silver. Mucicarmine is especially useful as it can stain the mucinous capsule pinkish red and typically does not stain other pathogenic fungi.[12] Capsule-deficient organisms can lead to considerable difficulties in diagnosis given the organisms can vary in size and may mimic *H capsulatum* or *B dermatitidis*. The Fontana-Masson stain is a valuable tool in identifying capsule-deficient organisms, as melanin is found in *Cryptococcus* cell walls; thus, positive staining excludes *H capsulatum* and *B dermatitidis*.[13]

Cutaneous foreign body granuloma, which refers to a granulomatous inflammatory reaction to a foreign body in the skin, is another differential diagnosis that is important to distinguish from cutaneous cryptococcosis. On histology, a collection of histiocytes surround the inert material, forming giant cells without an immune response (Figure 3).[10] In contrast, granulomas caused by infectious etiologies (eg, *Cryptococcus* species) have an associated adaptive immune response and can be further classified as necrotizing or non-necrotizing. Necrotizing granulomas have a distinct central necrosis with a surrounding lymphohistiocytic reaction with peripheral chronic inflammation.[10]

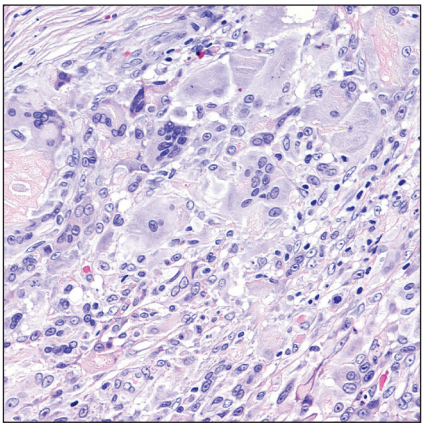

FIGURE 3. Foreign body granuloma in a pilomatricoma showing granulomatous inflammation with multiple foreign body type giant cells (H&E, original magnification ×40).

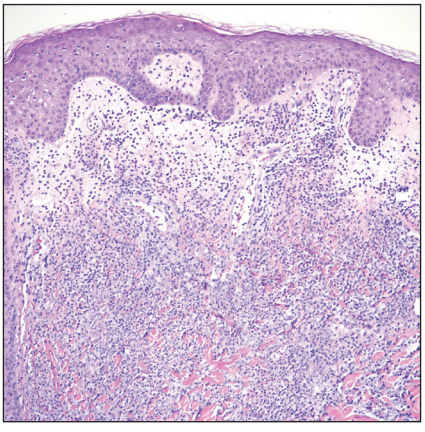

FIGURE 4. Sweet syndrome showing papillary dermal edema with dense mixed interstitial histiocytic infiltrate and numerous neutrophils (H&E, original magnification ×10).

Sweet syndrome is another mimicker of cutaneous cryptococcosis. A histologic variant of Sweet syndrome has been reported that has characteristic cutaneous lesions clinically but shows basophilic bodies with a surrounding halo on pathology that can be mistaken for *Cryptococcus* yeast. Classic histopathology of Sweet syndrome features papillary dermal edema with neutrophil or histiocyte-like inflammatory infiltrate (Figure 4). Identification of Sweet syndrome can be aided by positive myeloperoxidase staining and negative periodic acid–Schiff staining.[14,15]

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