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Journal

Dermatology Online Journal, 19(10)

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Publication Date

2013

DOI

10.5070/D31910020024

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Case Presentation

A Polymorphic, Mucocutaneous Eruption in a Patient with End-Stage Renal Disease

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Dermatology Online Journal 19 (10): 7

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Abstract:

An 81-year-old man is presented who developed cryptococcal infection after treatment for *Clostridium difficile* infection.

Keywords: Cryptococcus, Fungal Infection

Case synopsis:

An 81-year-old man was hospitalized for severe diarrhea, a fever of 102°F, and a WBC count of 18,000 per microliter. Fecal culture was positive for *Clostridium difficile*, which was consistent with his recurrent *C. difficile* colitis. In addition to being on hemodialysis for end-stage renal disease, his past medical history was significant for hypertension, hyperlipidemia, coronary artery disease, congestive heart failure, hypothyroidism, and benign prostatic hyperplasia. After several days of IV metronidazole and PO vancomycin, his fever and diarrhea resolved, and he was discharged with an oral course of the same regimen to complete treatment at home.

One week after hospital discharge, the patient developed cutaneous nodules on the face, scalp, trunk and groin, as well as hemorrhagic bullae on the fingers, dorsal and palmar hands, and tongue (Figs. 1 and 2). He was re-admitted to the hospital for evaluation. Aside from decreased oral intake related to pain associated with the tongue lesion, he had no other complaints and was afebrile. He had no diarrhea during his re-admission. Vital signs were within normal limits. His medications included oral metronidazole, vancomycin, clonidine, digoxin, enoxaparin, iron sulfate, fluoxetine, metoprolol, protonix, levothyroxine, hydralazine, lanoxin, and darbepoietin alfa. Vancomycin was promptly discontinued for concern of drug eruption. He had a normal complete blood count with differential and his chest radiograph was clear. His stool toxin assay was negative for *C. difficile* toxin and a cerebrospinal fluid (CSF) culture examination did not yield any microorganisms. A skin biopsy was done (Figure 3), which revealed cryptococcal organisms.



Figure 1. Cutaneous nodules on the face and scalp.



Figure 2. A clean-based ulcer with surrounding edema on the lateral tongue.

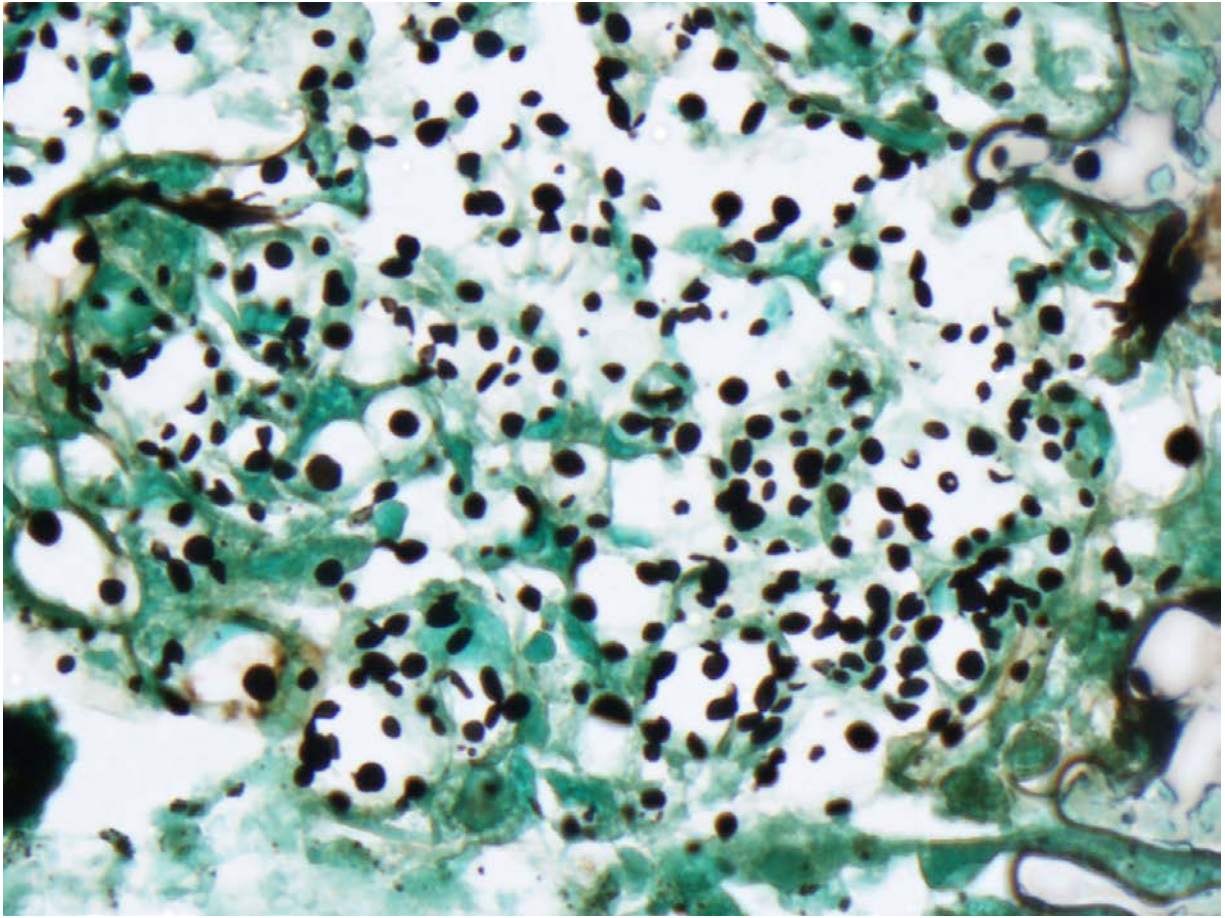


Figure 3. Gomori methenamine silver stain at 150x demonstrating cryptococcal organisms.

Discussion

Biopsy of one of the nodules revealed a neutrophilic and granulomatous reaction in the dermis and cryptococcal organisms surrounded by gelatinous spaces in the stroma—histological features characteristic of *Cryptococcus neoformans* infection. *C. neoformans* is an encapsulated fungus found in soil that is contaminated by bird droppings. Infection is usually acquired through inhalation of basidiospores and/or desiccated *C. neoformans* cells but can also occur through direct contact following trauma or transplantation of infected organs [1,2]. *C. neoformans* is an opportunistic pathogen, frequently infecting patients who are HIV positive, undergoing immunosuppressive therapy, or suffering from leukemia [3].

C. neoformans infection most commonly manifests in the CNS or the respiratory tract of immunocompromised individuals. The clinical presentation is highly dependent on the patient's immune status and the site of infection, but the most common as well as most dangerous manifestation of the disease is meningitis. In addition, pulmonary disease may often be initially asymptomatic but can progress to chronic pneumonia and eventually to adult respiratory distress syndrome (ARDS). Fever, cough, and chest pain may also be present. Extrapulmonary and extraneural infections are associated with a worse prognosis because atypical presentations usually cause a delay in diagnosis and treatment [4].

The skin and mucosa are the third most commonly affected sites and occur in 10-15% of individuals with disseminated Cryptococcus [1,5]. Serotype D of *C. neoformans* appears to have the strongest association with cutaneous disease [6]. In cases of systemic disease, cutaneous/mucocutaneous infection may be primary or secondary, manifesting as multiple, polymorphic lesions [1,7]. The differential diagnosis includes bacterial cellulitis, molluscum contagiosum, herpetic whitlow, pyoderma gangrenosum, vasculitis, and necrotizing fasciitis [8,9,10]. Primary cutaneous/mucocutaneous disease is considered a distinct entity, and those affected are typically older, live in rural areas, and have no underlying disease. A history of skin injury, outdoor activity, and exposure to bird droppings are associated risk factors [7].

The diagnosis of cryptococcal infection is established through the identification of the microorganism by culture or histopathologic examination [11]. Depending on the site of involvement, lumbar puncture and/or cultures are necessary to identify the organism. Prompt treatment is crucial in decreasing mortality, especially in HIV/AIDS patients. Cryptococcal organisms are globose and exhibit narrow-based multilateral budding; pseudohyphae are absent. India ink stain allows for easy visualization of

the organism from the cerebrospinal fluid. Mucicarmine stains, which are specific for the abundant polysaccharide capsule, produce a characteristic pink color that allows differentiation from other endemic fungi in tissue sections. Other non-specific stains, such as Gomori methenamine silver (GMS), can also be helpful in identifying the organism. Serum cryptococcal antigen is more likely to be positive in immunosuppressed individuals, but a negative test—which was observed in our patient—does not preclude the diagnosis [12].

According to the most recent guidelines for the treatment of non-meningeal, non-pulmonary cryptococcosis set forth by the Infectious Disease Society of America (IDSA), cryptococemia is defined as involvement of at least two noncontiguous sites or evidence of high fungal burden. Morbidity associated with disseminated cryptococcal infection includes end organ damage. Cryptococemia should be treated as CNS disease with an induction phase of four weeks with amphotericin B deoxycholate (0.7–1.0 mg/kg per day) plus flucytosine (100 mg/kg per day), followed by a four-week consolidation phase of fluconazole 400 mg per day, and 6-12 months of maintenance therapy with fluconazole 200 mg QD [13]. Alternative regimens exist to account for variations between individuals' symptoms, risk for therapeutic failure, and renal status. If CNS disease is ruled out, fungemia is not present, infection occurs at single site, and there are no immunosuppressive risk factors, the preferred treatment is fluconazole 400 mg (6mg/kg) daily orally for 6-12 months [13]. Since our patient met nearly all of these conditions, he was treated with oral fluconazole 400 mg daily. He experienced significant improvement of skin lesions within the initial weeks of therapy. Shortly thereafter, the patient expired from sepsis after developing an infection of his tunneled catheter.

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