



Cryptococcal Cellulitis in a Patient Immunocompromised Secondary to Cirrhosis

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Abstract

Cryptococcal cellulitis is a rare dermatologic diagnosis most often seen in immunocompromised patients. We present a case of disseminated *Cryptococcus* presenting as cellulitis in a patient with decompensated cirrhosis. We discuss various presentations of *Cryptococcus* in the skin, both as primary and disseminated disease.

Introduction

Cryptococcus is an encapsulated yeast of which five serotypes have been identified to date. *Var neoformans*, more common in immunocompromised individuals, has been isolated from bird feces, soil, plants, and contaminated foods, while *var gattii*, more common in immunocompetent individuals, is mostly located in tropical and subtropical regions in association with eucalyptus trees¹. Causes of an immunocompromised state associated with cryptococcal infection include immunosuppressive medications, malignancy, HIV, and solid organ transplant, among others².

An individual becomes infected by *Cryptococcus* after inhalation into the lungs³. Roughly one-third of immunocompetent patients who develop pulmonary cryptococcal infections will be asymptomatic, while roughly half will have chest pain and cough⁴. The extrapulmonary findings of *Cryptococcus* are most commonly seen after hematogenous spread from the lungs to other organs (central nervous system (CNS), bone, skin), with roughly 10-20% of disseminated cases showing skin involvement⁵. Of note, cutaneous *Cryptococcus* may precede systemic symptoms by as long as 8 months⁶. Rarely, an individual can acquire primary cutaneous cryptococcosis infection secondary to direct inoculation from trauma to the skin, with no evidence of disseminated infection⁷.

The objective of this paper is to report a case of disseminated cutaneous cryptococcal infection in a patient with decompensated cirrhosis.

Case Report

A 64-year-old male with past medical history of ulcerative colitis, decompensated cirrhosis secondary to primary sclerosing cholangitis, hepatocellular carcinoma status-post chemoembolization (on list for liver transplant, MELD-Na 22), and hypertension was admitted to the hospital with a 3-week history of a painful and warm erythematous plaques on his bilateral thighs. The plaques were expanding in size despite one week of

cephalexin. Notable medications included mesalamine, lactulose, rifaximin, and spironolactone. Upon admission, labs revealed a white blood cell (WBC) count of $5.5 \times 10^3/\mu\text{L}$, platelets $84 \times 10^3/\mu\text{L}$, and INR 1.4. A CT of the chest/abdomen/pelvis was significant for new patchy ground-glass and nodular opacities in the upper lungs. A duplex ultrasound (US) of the lower extremity deep venous system was negative for deep venous thrombosis. The patient was admitted for presumed cellulitis and started on intravenous vancomycin. Dermatology was consulted to further evaluate the patient.

On dermatologic examination, the patient had ill-defined, indurated, erythematous plaques on the bilateral medial thighs (Figure 1a, Figure 1b). Differential diagnosis included superficial thrombophlebitis, cellulitis, eosinophilic cellulitis, and cryptococcal cellulitis. Duplex US was negative for superficial thrombophlebitis. Given the bilateral nature of the plaques and induration on exam, along with the immunosuppressed status of the patient and upper lung ground glass opacities, a more extensive work-up was performed along with a punch biopsy. Serum cryptococcal antigen was obtained and returned at 1:320, significantly raising concern for a cryptococcal infection. Due to the propensity of *Cryptococcus* to disseminate to the CNS, a lumbar puncture was performed. Cerebrospinal fluid (CSF) cell count was notable for WBC $14/\text{mm}^3$ (normal $0-8/\text{mm}^3$, 42% polymorphonuclears (normal 0-6%), 17% lymphocytes (normal 40-80%). CSF cryptococcal antigen and fungal culture (1 of 2) were positive for *Cryptococcus neoformans*.

Punch biopsy from an erythematous plaque present

on the right medial thigh revealed a superficial and deep dermal mixed inflammatory infiltrate composed of lymphocytes, histiocytes, and occasional neutrophils (Figure 2) in addition to numerous yeast-shaped fungal organisms with GMS stain (Figure 3) that also stained positive with mucicarmine (Figure 4). The histologic features were consistent with *Cryptococcus neoformans*, confirming the diagnosis of disseminated cryptococcal cellulitis and meningitis.

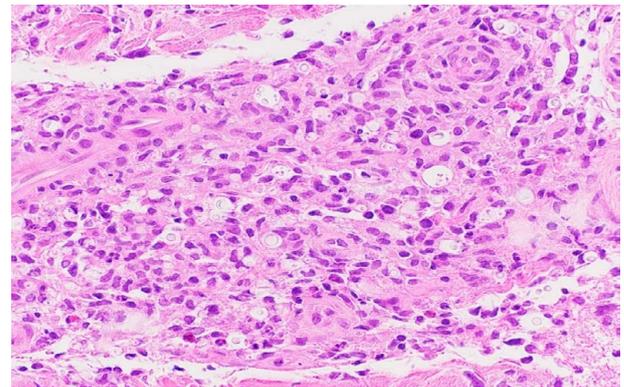


Figure 2: Hematoxylin and eosin (H&E) stain revealing numerous variable sized yeasts contained within clear spaces surrounded by a predominantly mononuclear infiltrate.

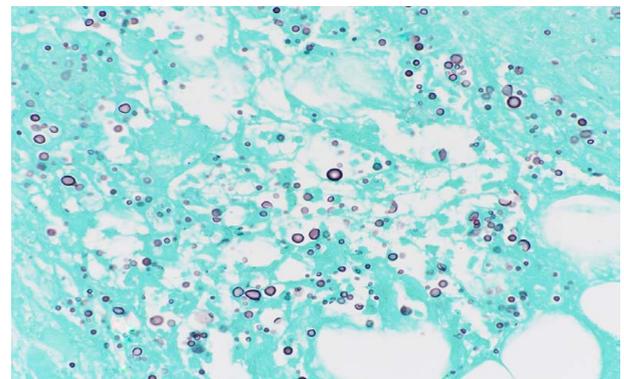


Figure 3: GMS stain showing gray-black reaction with the fungal wall.

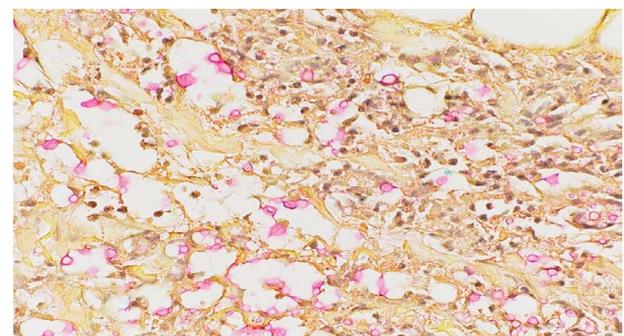


Figure 4: Mucicarmine stain showing pink-to-red staining of the mucinous capsule composed of acid mucopolysaccharides.



Figure 1(a): Ill-defined, indurated, erythematous plaques on the bilateral medial thighs.



Figure 1(b): Close-up view of erythematous plaque present on the right medial thigh.

The erythema and induration of the plaques on the thighs rapidly improved with clobetasol (for possible contact versus stasis dermatitis) and showed further improvement with amphotericin (5 mg/kg IV every 24 hours) and flucytosine (25 mg/kg IV every 6 hours). Two weeks after admission, the patient developed acute kidney injury likely secondary to amphotericin administration. Pulmonary edema (noted on serial X-rays) developed and lead to acute hypoxic respiratory failure 16 days after admission. Despite diuresis with furosemide, he was admitted to the intensive care unit with acute hypoxic respiratory failure and intubated. Shortly after, the family of the patient opted for comfort measures, and the patient was compassionately extubated. Within hours of extubation, the patient passed away. The cause of death was acute respiratory failure with hypoxia in the setting of pulmonary edema due to acute kidney injury.

Discussion

Cryptococcal cellulitis is a rare diagnosis secondary to primary or disseminated infection. Physical exam findings can help differentiate skin lesions caused by disseminated infection from those caused by primary cutaneous cryptococcosis. Disseminated *Cryptococcus* appears most commonly as scattered umbilical papules (similar to molluscum contagiosum)⁷, while primary cutaneous cryptococcosis skin lesions are usually found on unclothed areas (exposed to trauma/inoculation), are solitary, and most often resemble cellulitis⁷. Primary cutaneous cryptococcosis has been associated with a wide variety of lesions, including papules, nodules, pustules, abscesses, subcutaneous swellings, and ulceration. Cutaneous cryptococcal infection should be on the differential for cellulitis in atypical locations, containing ulceration, or unresponsive to treatment. In this case, the bilateral nature of the erythematous plaques made a diagnosis of cellulitis unlikely and led the dermatology consult team to seek alternative diagnoses.

In the above case, immunosuppression was multifactorial. Decompensated cirrhosis was the most likely contributing factor to immunosuppression. Individuals with decompensated liver disease have a 24-fold increase in risk of cryptococemia and cryptococcal meningitis and make up 21-36% of cases of *Cryptococcus* in non-HIV patients⁸⁻¹². Cirrhosis results in immunosuppression due to defects in the host immune response, including phagocyte dysfunction, decreased antibody and immunoglobulin production, complement deficiency, and impaired cell-mediated immunity⁸⁻¹¹. The hypothesis of pulmonary *Cryptococcus* reactivation from immunosuppression is supported by the fact that the majority of liver transplant patients have cryptococcal antibodies prior to transplant^{3,13}. Mesalamine's mechanism is poorly understood, although it likely has anti-inflammatory effects (reduction of

pro-inflammatory prostaglandins and leukotrienes)¹⁴. However, mesalamine usage showed no association with increased infection (odds ratio 1.0, p = 0.94) in one study of patients with ulcerative colitis and Crohn's disease¹⁵. Although this patient had a history of hepatocellular carcinoma, it was treated roughly one-year prior with chemoembolization, thus this was likely noncontributory to the immunosuppressed state. Lastly, ulcerative colitis and primary sclerosing cholangitis are more often associated with immune system activation^{16,17}.

Management of cryptococcal infection varies upon disease severity, underlying immune status and comorbid conditions (HIV, organ transplant history), and presence or absence of dissemination, with medication regimens including induction, consolidation, and maintenance therapies¹⁸. Despite defined treatment algorithms, disseminated *Cryptococcus* has been associated with high mortality rates (63% in one case series of 30 HIV-uninfected patients with disseminated disease (mean survival 21 days))¹⁹.

In this case, we report a patient with cirrhosis, ulcerative colitis, and primary sclerosing cholangitis who was diagnosed with disseminated (CSF, serum, skin) cryptococcal infection and subsequently passed from disease management complications. Early recognition of cellulitis not responding to conventional management, especially in immunosuppressed patients, should point the clinician to consider revisiting the diagnosis. This is key in diagnosis of *Cryptococcus*.

Conflict of Interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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