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Case Report
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Primary Cryptococcal Cellulitis in an Immunocompetent Individual via Traumatic Inoculation

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Abstract

Background: *Cryptococcus gattii is a pathogenic fungus that poses a significant threat to immunocompromised populations, with the most classic presentation being life-threatening CNS disease such as meningitis. Cryptococcosis in immunocompetent individuals is usually asymptomatic or results in mild illness. We present the case of a 77-year-old immunocompetent male with severe necrotizing cellulitis found to be a rare primary presentation of Cryptococcus gattii.*

Case report: *A 77-year-old male with a past medical history significant for chronic kidney disease presented to the emergency room for evaluation of progressive left-hand cellulitis that had been developing for 10 days. He had no history of immunocompromise and no central nervous system complaints. The patient noticed an unexplained, small lesion on the dorsum of his left hand followed by progressive swelling over the next day for which he was treated with empiric antibiotics. The condition progressed despite daily oral antibiotics and he was hospitalized as the cellulitis had worsened significantly with evidence of hemorrhagic bulla and swelling of his entire extremity. The wound was debrided surgically with intraoperative cultures yielding Cryptococcus gattii. The patient was treated with antifungal medication, multiple debridements, and skin grafting.*

Conclusions: *Serious cryptococcal infection in immunocompetent hosts remains a rare presentation. Cryptococcal cellulitis, a rare manifestation in its own right, is sometimes a manifestation of disseminated cryptococcal disease found in immunocompromised individuals. This report supports new thought that Cryptococcus gattii may be more virulent and pathogenic in immunocompetent individuals than Cryptococcus neoformans. Clinicians should rule out underlying immunocompromise in the setting of confirmed cryptococcal cellulitis*

Keywords: Cellulitis, Cryptococcal Infection, Cryptococcus Gattii

Abbreviations

CNS: Central Nervous System
CT: Computed Tomographic (Ct) Scan
AIDS: Acquired Immune Deficiency Syndrome
PCC: Primary Cutaneous Cryptococcosis

Introduction

Cryptococcus gattii, formerly classified as a subgroup of Cryptococcus neoformans, is a pathogenic fungus that has posed a significant health risk to immunocompromised individuals worldwide and is a feared cause of often fatal meningoencephalitis. Transmission is most frequent in tropical and subtropical climates and occurs when it is inhaled from the environment and the fungus thereafter colonizes the lungs [1, 2]. In immunocompromised patients, Cryptococcus gattii can evade host defenses with its virulence factors and migrate into the vascular tree, across the blood-brain barrier, and into the central nervous system (CNS) [1-4]. CNS complications are severe and devastating with meningoencephalitis secondary to cryptococcal CNS invasion being fatal without prompt, aggressive, and long-term

antifungal therapy [3]. Patients who survive often still have persistent residual neurological deficits [1].

Although Cryptococcal infections are notorious for rapidly fatal meningitis in those who are immunocompromised, here we detail the case of a 77-year-old immunocompetent male with severe necrotizing cellulitis that was found to be a rare primary presentation of Cryptococcus gattii and determined to be secondary to traumatic inoculation.

Case Presentation

A 77-year-old male with a past medical history significant for chronic kidney disease, hyperlipidemia, hypertension, and benign familial tremor presented to the emergency room for evaluation of left-hand pain, erythema, and swelling that had been developing for more than a week. The patient was playing golf on vacation 10 days prior and noticed a small lesion with a pustule on the dorsum of his left hand. The next day he did some yard work and over that day he noticed the swelling progressively worsened with his hand becoming more erythematous and painful. He denied sustaining any injuries, trauma, wounds cuts or known insect bites. The day after, he disembarked for a cruise to Key West, and at his first stop, he went to an urgent care center (Figure 1) at which point he was started on oral amoxicillin-clavulanate and clindamycin. The patient did not have improvement in his symptoms over the next 7 days of his cruise. (Figure 2) When he returned from his vacation, he visited his primary care physician who requested he present to the emergency room for further evaluation.

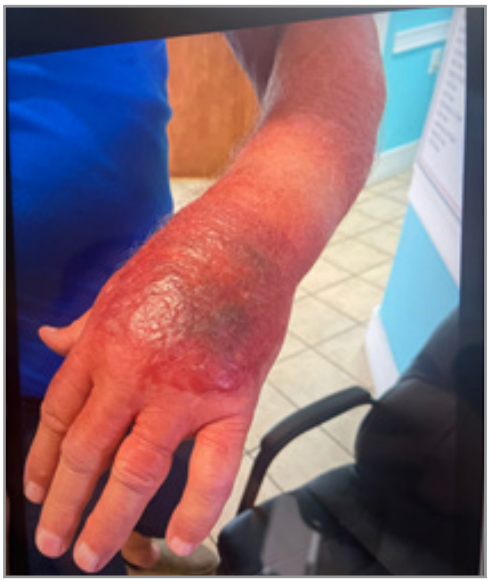

Figure 1: Dorsum of the left hand and arm approximately 3-4 days after first noticing the first-hand lesion

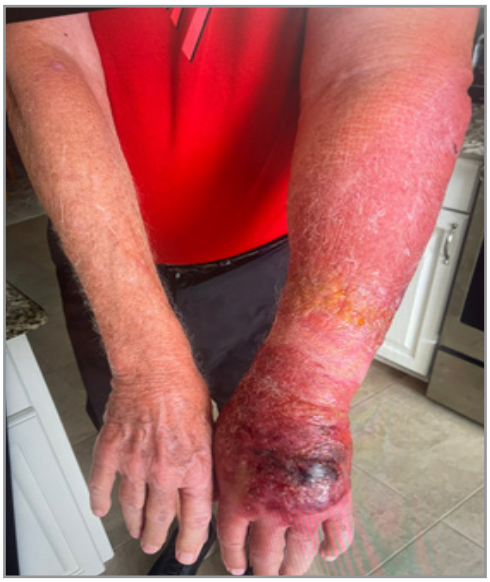

Figure 2: Upper extremities on Day 10 immediately before presentation to his primary care provider. The left arm is significantly more swollen than the right arm with erythema tracking proximally over the majority of the forearm. A large hemorrhagic bulla is noted over the dorsum of the left hand and is presumed to be the site of inoculation

On evaluation in the emergency department, the patient reported drainage from the left hand and noted that erythema and edema had been progressing proximally over his entire forearm. He denied any fever, chills, cough, chest pain, shortness of breath, nausea, vomiting, dysuria, hematuria, constipation, or diarrhea. He denied bug or animal bites, and except for swimming and yard work, denied any other exposures. He was afebrile upon presentation, with vitals significant for a blood pressure of 172/88mmHg. His vitals were otherwise unremarkable. On physical exam, the left hand and arm were warm, edematous, and erythematous, extending proximally to the elbow on the dorsal surface of the forearm. The patient was unable to clench his fingers into a fist. Pulses were palpable and there was no concern for compartment syndrome. Open wounds were noted on the dorsum of the hand and on the forearm with draining serosanguinous discharge.

Laboratory evaluation was significant for white blood cell count (WBC) within normal limits at 7.2 x 103, (4.4 to 10.5 x 103). Erythrocyte sedimentation rate (ESR) was found to be elevated at 41mm/hr (0 to 22mm/hr), along with the C-reactive protein elevated to 6.6 (≤ 1 mg/dL). The lactic acid level was not elevated. The human immunodeficiency virus (HIV) test was negative. Blood cultures were drawn which did not yield any growth. Fungal, acid fast bacteria, aerobic, and anaerobic cultures were obtained from the wound. The patient received an x-ray of the left forearm which was negative for foreign body, acute fracture, or dislocation, and did not reveal changes consistent with osteomyelitis. A computed tomographic (CT) scan of the upper extremity without contrast was consistent with cellulitis, revealing diffuse skin thickening with near circumferential confluent subcutaneous soft tissue edema throughout the forearm, wrist, and hand. Soft tissue edema was seen extending into the investing fascia. No gas was seen. No intramuscular edema or discrete

drainable fluid collections were visualized. Empiric vancomycin and cefepime were started and the patient was admitted for further treatment.

The surgery team evaluated the cellulitis and wounds and the patient underwent incision and drainage. Hand and forearm necrosis and purulence were noted without bone, joint, or tendon involvement. A wound vacuum was placed and the patient underwent serial debridements to prepare the arm and hand for reconstruction. After the second debridement, all cultures drawn remained negative except for aerobic cultures which finally grew Cryptococcus gattii. Vancomycin and cefepime were discontinued, and the patient were started on voriconazole. Ultimately, this infection was determined to be from traumatic inoculation. After four debridement's, the wounds were successfully debrided and he returned to the operating room for the fifth and final time for skin grafting. (Figure 3) The patient was discharged with oral voriconazole and completed a 4-week course. The patient has followed up regularly as an outpatient and has been gradually recovering. He states he is continuing to improve and is eager to return to physical activities as permitted.

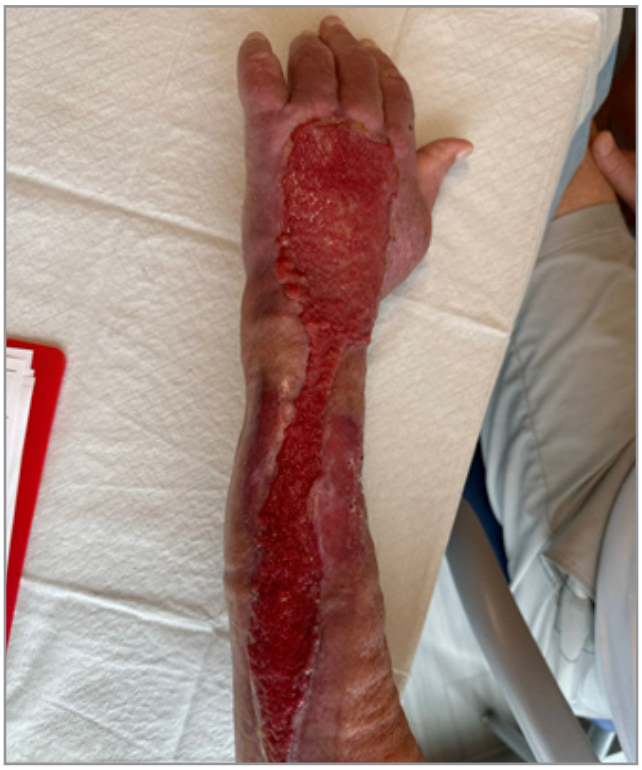

Figure 3: After skin grafting on the left hand and arm.

Discussion

Cryptococcus is an encapsulated yeast with several different serotypes that is most commonly associated with infection and disease in immunocompromised individuals. Until recently, the five subgroups of Cryptococcus were classified as variants of Cryptococcus neoformans, i.e., Cryptococcus neoformans var gattii [4]. The lineage of Cryptococcus neoformans and Cryptococcus gattii has been controversial [4]. However, a publication in May 2015 clarified this debate via phylogenetic analysis and genotypic studies and supported a seven-species concept that had been presented in the past. Cryptococcus gattii itself was divided into multiple species from this report [5]. These species are Cryptococcus gattii, Cryptococcus deuterogattii, Cryptococcus tetragattii, and Cryptococcus decagattii [5].

Cryptococcus gattii is often found in tropical and subtropical climates in bird droppings, soil, and eucalyptus trees. [1-4] Infection by the pathogenic fungus most often occurs after it has been inhaled by an individual from the environment and colonizes the lungs [1-4]. From here, the fungus is capable of evading the host's immune response through its polysaccharide capsule and secretion of enzymes [1]. In healthy individuals, fungal infection is often cleared by macrophages; however, in immunocompromised hosts, the pathogen may survive within the dysfunctional immune cells [1]. It is rare for cryptococcal infection to occur in immunocompetent individuals and usually results in mild flu-like illness or even more uncommonly cryptococcal pneumonia at its most severe [1]. Cutaneous involvement from cryptococcal infection is very uncommon and occurs in only 10-15% of cases with the vast majority of reports being manifestations of disseminated disease in immunocompromised individuals. Immunocompromising conditions that are most associated with cryptococcosis include those suffering from acquired immune deficiency syndrome (AIDS) and individuals who are receiving solid organ transplants [6-9].

Cryptococcal cellulitis, although most commonly associated with immunocompromised hosts and disseminated cryptococcosis, remains a rare presentation. In even fewer cases it may be the only indication or an early manifestation of disseminated cryptococcosis in the setting of immunocompromise, making early identification critical as disseminated cryptococcosis is

life-threatening and rapidly fatal if left untreated [8]. Primary cutaneous cryptococcosis (PCC) as seen in our patient is a rare outcome of traumatic inoculation from Cryptococcus neoformans with few reports in the literature [10]. The disease course is often similar to the one seen in our patient, with rapidly progressive cellulitis that fails to respond to antibiotic therapy [11]. The cellulitis in PCC is severe, rapidly progressive, and ulcerative with a large majority of reported cases occurring in those with renal disease, and is consistent with our patient's history of chronic kidney disease. Treatment generally involves antifungal medication such as itraconazole or fluconazole as well as direct debridement in the most severe cases such as our patient [4-11].

As there have been recent changes to the classification of Cryptococcus spp., it can only be speculated whether certain previous reports of cryptococcal cellulitis attributed to Cryptococcus neoformans may actually have been caused by Cryptococcus gatti due to previous nomenclature. The differences in the two are being increasingly delineated with some reports noting that Cryptococcus gattii appears to cause more infections in immunocompetent hosts than Cryptoocccus neoformans. Additionally, the predilection this fungus appears to have for individuals with kidney dysfunction is so far unexplained [12]. Further study is required as this is an emerging area of the literature with new clinical implications [4]. Nonetheless, from a diagnostic and therapeutic standpoint, both yeast species are managed identically.

Conclusion

It is exceedingly rare for cryptococcal infection to occur in immunocompetent individuals, however this remains possible as seen in our patient. Even in cryptococcal cellulitis, a rare complication, the vast majority of reports are manifestations of disseminated disease seen in immunocompromised individuals. New findings suggest that Cryptococcus neoformans and Cryptococcus gattii are not as similar as once thought, and this report supports new thought that Cryptococcus gattii may be more virulent and pathogenic in immunocompetent individuals than Cryptococcus neoformans. It is important for clinicians, particularly those in the outpatient setting, to keep rare causes of cellulitis on their differential and to provide clear instructions to patients for things to bear in mind in the event that their cellulitis worsens to facilitate prompt return to clinic for reevaluation in the setting of potential antibiotic failure, and to rule out underlying immunocompromise in the setting of confirmed cryptococcal cellulitis.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article, no sources of support, no funding. All authors had access to the data and a role in writing the manuscript, no disclaimers

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