BRIEF ARTICLE

Primary Cutaneous Cryptococcus Following Traumatic Exposure: A Case Report and Retrospective Analysis

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ABSTRACT

Primary cutaneous cryptococcus (PCC) is a form of *Cryptococcal neoformans* infection characterized by localized cutaneous colonization and proliferation. In this case study, we present PCC occurring following a previous trauma in a 77-year-old male with a history of renal organ transplant maintained by immunosuppressive therapy. Colonies of *C. neoformans* were successfully identified during a secondary workup after the patient had been misdiagnosed. Despite the treatment delay, complete remission was achieved through aggressive antifungal therapy. Our case highlights common clinical pitfalls that contribute to the prolonged diagnosis of PCC. Our findings and retrospective analysis underscore commonalities in disease presentation, such as high-risk patient populations, transmission routes, and associated symptoms. Integrating these insights into clinical practice may increase awareness and improve patient outcomes.

INTRODUCTION

Primary Cutaneous Cryptococcus (PCC) is a rare presentation of *Cryptococcus neoformans*, where cutaneous lesions form through skin inoculation rather than underlying dissemination. Infection occurs infrequently in the general population and is commonly seen in the setting of underlying immunosuppression. While multiple cases of PCC have been reported in the literature, the disease lacks a well-defined clinical course, and its symptoms, though overlapping are often nonspecific, requiring a large differential. Commonly, the disease occurs in Human Immunodeficiency Virus (HIV)-positive immunocompromised hosts with pulmonary transmission routes.[1] This report documents a 77-year-old HIV-negative, immunocompromised male who developed PCC following trauma.

CASE REPORT

A 77-year-old male veterinarian with a history of a renal transplant and immunosuppression presented with a painful, erythematous plaque that developed four days prior. The injury occurred following a tree-branch-induced laceration, and on examination, a five-by-five cm ulcerated plaque with seropurulent exudate (**Figure 1**) was noted on the ventral surface of the right forearm. Two four-mm punch biopsies were performed

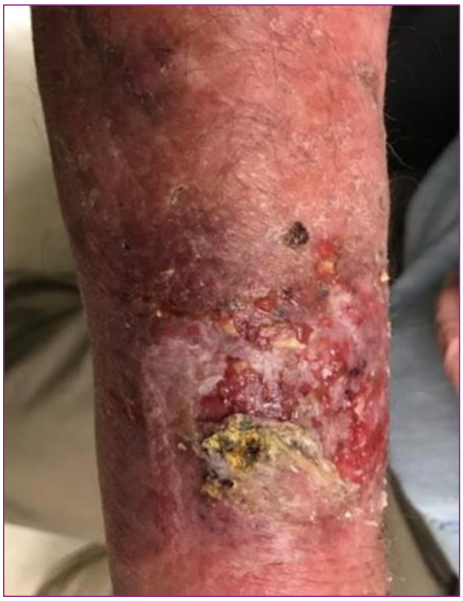

Figure 1. Ulcerated lesion on the right forearm with erythema, lateral view.

(one sent for H&E and the other sent for tissue culture), and the patient began a broad-spectrum empiric therapy of ciprofloxacin (500 mg orally BID) for suspected bacterial cellulitis.

Histopathological findings identified small, narrow-based, budding yeasts thought to be *Histoplasma capsulatum*. Tissue culture revealed gelatinous colonies consistent with *C. neoformans*. The patient was urgently admitted to the ER, where two additional punch biopsies were performed. Repeat histopathology and tissue culture revealed thick mucoid capsules, underlying inflammation, and leukocytosis, again confirming *C. neoformans* infection (**Figure 2A-C).** A diagnosis of PCC was made, prompting the initiation of aggressive antifungal therapy, which consisted of an intravenous amphotericin B/flucytosine suspension, oral itraconazole, and intravenous vancomycin. The patient was closely monitored and achieved complete resolution six weeks after treatment initiation.

DISCUSSION

The development of *C. neoformans*-induced skin lesions is a rare clinical finding, typically indicating pulmonary dissemination or, less commonly, presenting as an isolated finding from direct inoculation.[2] While the time from exposure to dissemination is highly variable, the disease follows a fixed and fatal course, spreading to the central nervous system and inducing meningoencephalitis if left untreated.[3] Prompt identification of both cutaneous and disseminated cryptococcal infections is crucial to mitigate adverse outcomes. However, the nonspecific presentation of PCC in the absence of systemic symptoms often delays diagnosis longer than in cases of disseminated infection. Although PCC development is rare, literature-reported cases continue to rise, likely due to the organisms' ubiquitous environmental presence and the increase in immunosuppressive therapies.[2,4]

Today, delayed diagnosis often impedes clinical care. **Table 1** presents a capsule summary of PCC cases in nine HIV-negative hosts.[3,5-12] Affected individuals were predominantly male,[3,5-9,11,12] and underlying immunosuppression was present in 66% of

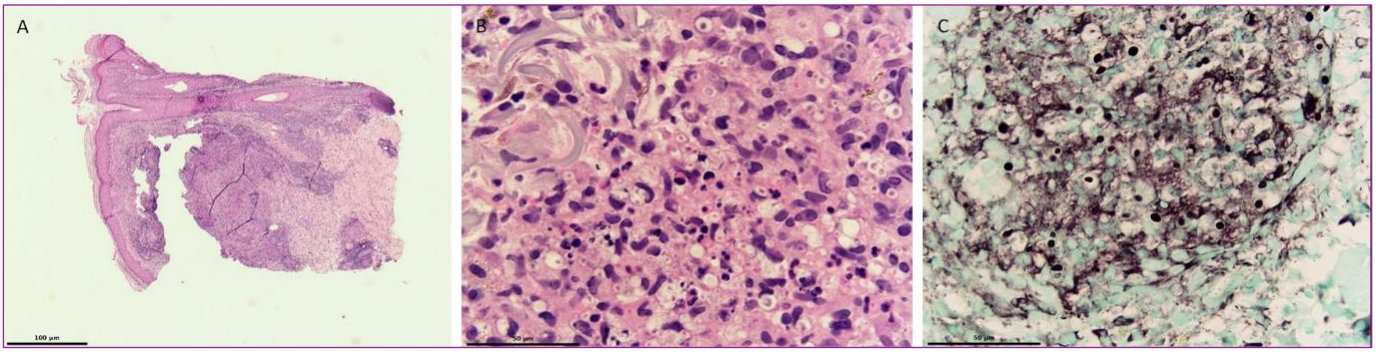

Figure 2. (A) Hematoxylin and eosin stain, low-power field (40x magnification). **(B)** Hematoxylin and eosin stain, high-power field (1000x magnification), showing ovoid yeast organisms with a clear halo-like capsule. **(C)** Grocott's methenamine silver stain, high-power field (1000x magnification), highlighting thick-walled, budding yeast with prominent round capsules.

identified cases. Studies noted an increased susceptibility among neutropenic hosts.[6,7,9-12] In this population, disease recognition is further complicated by the heightened risk of polymicrobial colonization. Despite these challenges, a consistent overlap in appearance was observed across all HIV-negative hosts, particularly the presence of confluent epidermal ulceration at infection site.[3,6-12] This finding, while suggestive of *C. neoformans*, lacks specificity as lesions are pleomorphic, making it difficult to discern PCC from other infections.

The non-diagnostic features exhibited by PCC pose a significant barrier to treatment, potentially resulting in an incorrect differential diagnosis and treatment delay. Misdiagnosis was common among cases of confirmed PCC. Lesions were frequently mistaken for cellulitis.[5-7,9] In instances where a patient presents with an isolated lesion, including a biopsy and comprehensive workup into initial patient assessment may prevent treatment delays. While histopathologic examination alone is often sufficient to identify *C. neoformans*,[5-7,9] our case demonstrates the need for multiple modalities, including bacterial, mycobacterial, and fungal cultures, to strengthen diagnostic certainty.

Physical examination findings should be interpreted in the context of the patient's history, as prior history can heighten the suspicion of possible PCC inoculation. Specifically, underlying immunosuppression increases the risk of colonization with PCC. The rapid growth is facilitated by the capsule's antiphagocytic properties, alongside localized capsule-induced immunosuppression.[5,8] Literature trends support neutropenia in disease predilection;[3,5-9,12] and also suggests overlap in transmission routes, with external trauma identified in seven out of nine case reports.[3,5-9,12] A history of immunosuppression and penetrating trauma should increase clinical suspicion and half the identified dataset matched this sequence of events.[6,7,9,12]

CONCLUSION

The pleomorphic presentation of PCC, combined with its low infectivity, frequently hinders early diagnosis during physical examination. Current clinical practice lacks a standardized protocol for confirming PCC infection, leaving clinicians to consider a broad differential to reach the diagnosis. By recognizing the clinical overlap among PCC cases and considering these findings in their

Table 1. Case Reports of Primary Cutaneous Cryptococcus in HIV-negative hosts.

Author, year	Age year	Sex	Immune Status	Location	Exposure Route	Symptoms	Diagnosis Delay	Treatment	Outcome
Christianson et al, 2003[5]	41	M	Immunocompetent	Hand	Hay bale puncture	No ulceration, erythema, pain, nodule formation	6 weeks	Surgical excision p.o. fluconazole	Complete resolution
Kerr et al, 2018[6]	68	M	Immunosuppressed	Arm	Trauma	Ulceration, erythema, swelling, suspected cellulitis	1 month	IV amphotericin B and flucytosine	Incomplete resolution
Souza et al 2021[3]	61	M	Immunocompetent	Forearm	Bird excoriation	Ulceration, erythema, pain, mucoid-like tumor	30 days	p.o. fluconazole	Complete resolution
Henderson et al, 2018[7]	69	M	Immunosuppressed	Arm	Traumatic fall	Ulceration, erythema, bullous edema, suspected cellulitis	2 weeks	p.o. fluconazole	Incomplete resolution
Amaral et al, 2016[8]	68	M	Immunocompetent	Forearm	Mortar bag handling	Ulceration, erythema, headache, nausea, nodule and plaque formation	30 days	IV amphotericin B p.o fluconazole	Complete resolution
Suranyi et al, 2003[9]	26	F	Immunosuppressed	Legs	River wading	Ulceration, erythema, pain, suspected cellulitis, fever, chills nausea, vomiting, plaque formation	1 month	IV amphotericin B and flucytosine	Complete resolution
Baumgarten et al, 2004[10]	57	M	Immunosuppressed	Thigh	Unknown	Ulceration, erythema, nodule formation	2 months	p.o fluconazole	Complete resolution

Devirgiliis et al, 2008[11]	78	M	Immunosuppressed	Forearm	Unknown	Ulceration, erythema, pruritis, pain, fever, abdominal pain, anorexia, nausea, patch formation	2 weeks	IV amphotericin B	Death
Vogelaers et al, 2008[12]	77	M	Immunosuppressed	Finger	Needle Perforation	Ulceration, erythema, pain, pustular formation	Unknown	IV amphotericin B p.o. fluconazole	Complete resolution
Current Case	77	M	Immunosuppressed	Forearm	Tree branch Laceration	Ulceration, erythema, pain, plaque formation, suspected cellulitis	4 days	p.o. itraconazole IV vancomycin IV amphotericin B and flucytosine	Complete resolution

practice, clinicians can potentially improve their patient outcomes.

Our limited dataset indicates that immunosuppressed patients with a history of significant trauma may benefit from a comprehensive *C. neoformans* work-up. While further research is warranted, by integrating this evaluation into the initial assessment (particularly tissue biopsy and tissue culture) physicians may substantially diminish treatment delays. This review highlights the need for increased suspicion of atypical infections (such as PCC) in immunosuppressed patients. The authors advocate maintaining a broad differential diagnosis for deep fungal infections, atypical mycobacterial infections, and other less commonly seen infections in the solid organ transplant population. Early diagnosis is critical and can be lifesaving. Analysis of the literature of reported case studies of PCC can help identify common threads and may improve early detection efforts.

Conflict of Interest Disclosures: None

Funding: None

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