Case Report

A Rare Case of Lingual Cryptococcosis Presented as A Tongue Nodule in An HIV-Positive Patient

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Cryptococcus is an opportunistic fungal infection that primarily affects those with advanced HIV/AIDS. Oral manifestations are rare, and involvement of the tongue is exceptionally uncommon. Here, we present a rare case of lingual cryptococcosis in a 30-year-old male, who underwent treatment for cryptococcal meningitis presented with a papillary-like mass on the tongue. Given his history of advanced HIV and former smoking, oral malignancy or infection was initially considered. A subsequent biopsy of the tongue nodule collected firm tan soft tissue fragments. Histologic evaluation of the mass on H&E staining revealed squamous epithelium with subepithelial tissue containing round to oval yeasts with thick mucoid capsules, amidst mild inflammation. Focal ulceration and bacterial colonies were present on the epithelial surface. No evidence of malignancy can be identified. Periodic Acid-Schiff (PAS) and Grocott Methenamine Silver (GMS) stains highlighted abundant fungal organisms. Mucicarmine decorated the highly characteristic gelatinous capsules with bright pink color, consistent with cryptococcosis. This rare case of disseminated cryptococcosis involving the tongue in an HIV-positive patient highlights the need to consider fungal infections in atypical oral lesions. Oral cryptococcosis is uncommon and can easily be mistaken for more common conditions, such as neoplasms or bacterial infections. Our findings underscore the importance of considering fungal infections in the differential diagnosis of atypical oral lesions in immunocompromised patients and reinforce the role of biopsy in guiding timely diagnosis and management.

[N A J Med Sci. 2025;18(1):024-027. DOI: 10.7156/najms.2025.1801024]

Key Words: *Cryptococcus, Cryptococcosis, HIV, tongue, mucicarmine stain*

INTRODUCTION

Cryptococcosis is a life-threatening opportunistic fungal infection caused by encapsulated yeasts of the genus Cryptococcus, primarily affecting individuals with weakened immune systems, particularly those with advanced HIV/AIDS.[1] The two major species responsible for human disease are Cryptococcus neoformans and Cryptococcus gattii. C. neoformans is more common globally and particularly affects patients with AIDS, while C. gattii can also infect immunocompetent hosts.[1]

Infection typically begins in the lungs following inhalation of environmental spores, with potential for hematogenous spread to the central nervous system, resulting in meningoencephalitis - the most common clinical manifestation. Disseminated disease may also involve the skin, bones, eyes, and, less frequently, mucous membranes.[1] Oral and mucocutaneous cryptococcal infections have rarely been documented in the literature. A review of the literature revealed seven cases of cryptococcal infection with oral manifestations prior to 2016: five of them occurred in HIV-positive and/or patients with AIDS, one in an immunosuppressed stem cell transplant recipient, and one in an immunocompetent host. The lesions were located in the palate (two cases), tongue (two cases), maxilla (one case), mandible (one case), and salivary glands (one case).[2] In a few case reports, tongue lesions have been the first sign of systemic disease in HIV-positive patients.[3]

Here, we report a rare case of lingual cryptococcosis in a patient with AIDS. This case emphasizes the need to consider fungal etiologies in the differential diagnosis of atypical oral lesions in immunocompromised individuals and highlights an uncommon presentation of a well-known opportunistic infection.

Received: 07/08/2025; Revised: 08/09/2025; Accepted: 08/10/2025
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CLINICAL PRESENTATION

A 47-year-old man with a history of advanced HIV, recently initiated on antiviral therapy (ARV) including Dolutegravir and Darunavir/Cobicistat, presented with shortness of breath and headache. Serum cryptococcus antigen titer was markedly elevated at 1:1024. After being admitted to the hospital, cerebral spinal fluid analysis revealed cryptococcus antigen titer at 1:2560 with organisms visualized on India ink, consistent with Cryptococcal meningitis. While computed tomography (CT) of head showed no evidence of acute intracranial pathology, CT imaging of the chest revealed scattered nodular and ground-glass airspace opacities throughout the lungs, suggesting concurrent cryptococcal pneumonia. Treatment with amphotericin B and flucytosine was promptly started. During systemic evaluation, a papillary-like mass was identified on the tongue, raising suspicion for a potential malignant process or an undiagnosed oral infection.

RESULTS

The pathology lab received approximately 2 mL of clear, colorless fluid, identified as CSF. Cytology showed rare lymphocytes and mononuclear cells with no evidence of malignant cells. Subsequently, two soft tan tissue fragments were submitted in buffered formalin and measured up to 0,7 cm in the longest dimension. Histology evaluation of the tissue on H&E stain revealed squamous epithelium overlying subepithelial tissue containing round to oval yeast forms with thick mucoid capsules (**Figures A and B**), amidst mild inflammation. Focal ulceration and bacterial colonies were also noted superficially. No evidence of malignancy could be identified. Special stains, including Periodic Acid-Schiff (PAS) and Grocott Methenamine Silver (GMS) stains (**Figures C and D**), highlighted abundant fungal organisms. Mucicarmine (**Figure E**) decorated the highly characteristic gelatinous capsules with a bright pink color, consistent with cryptococcosis.

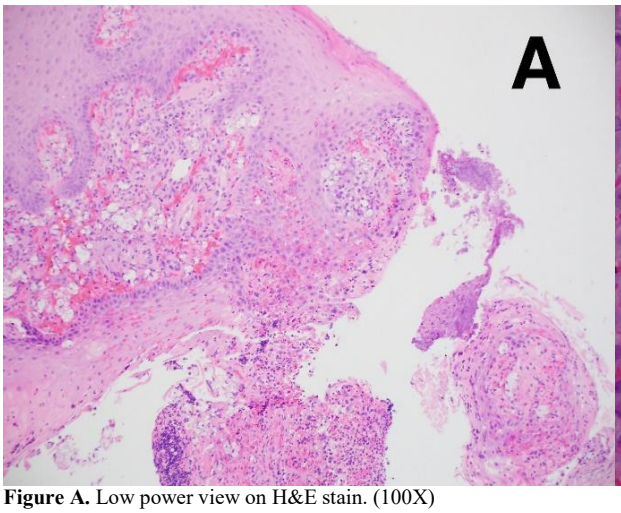

Figure A. Low power view on H&E stain. (100X)

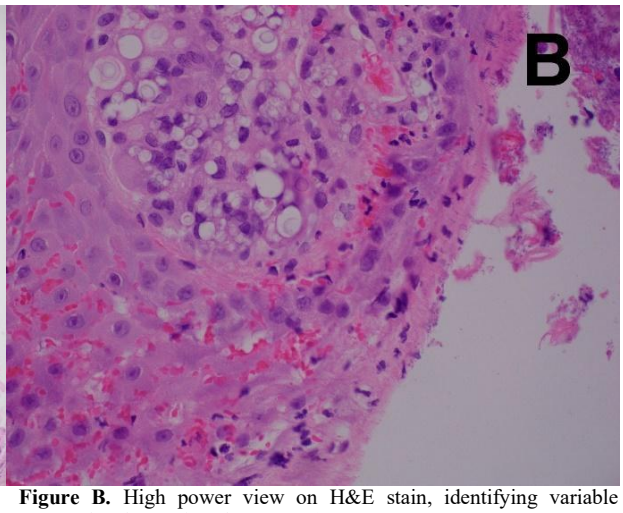

Figure B. High power view on H&E stain, identifying variable encapsulated yeast in submucosa. (400X)

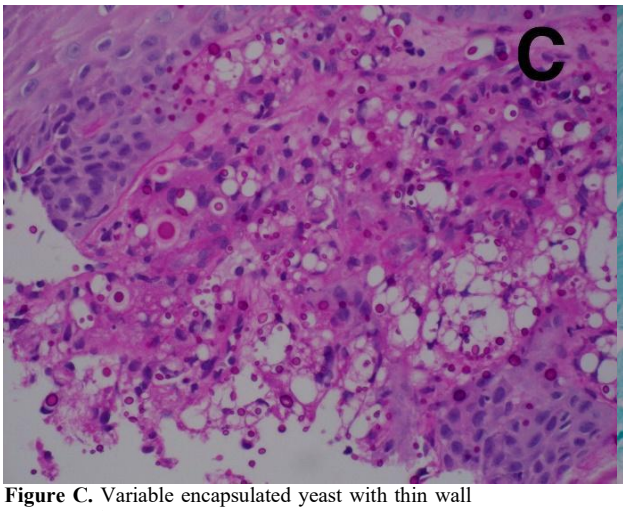

Figure C. Variable encapsulated yeast with thin wall on PAS stain.

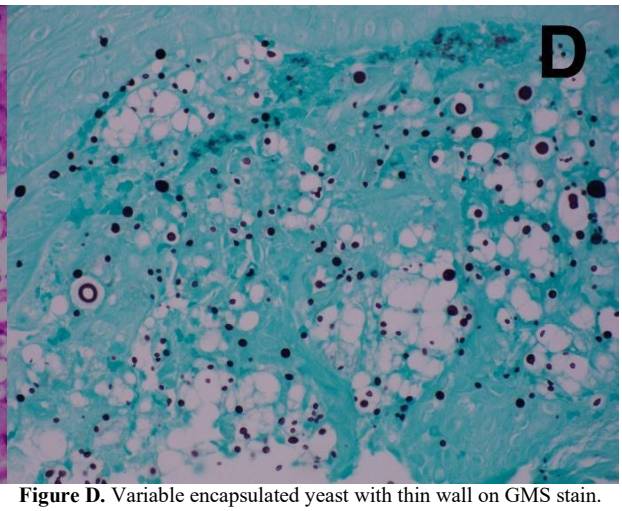

Figure D. Variable encapsulated yeast with thin wall on GMS stain.

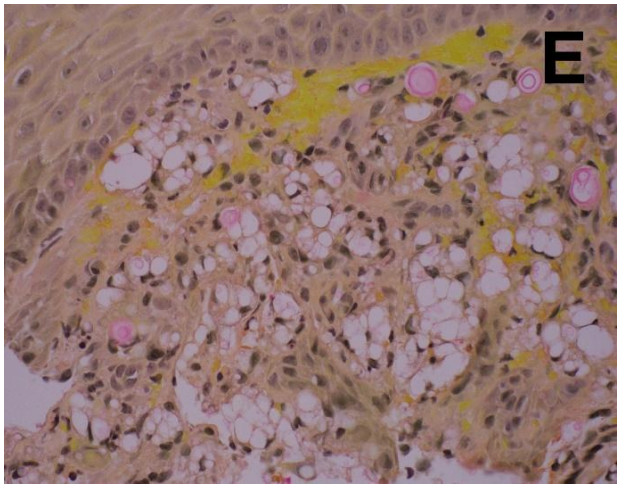

Figure E. Mucicarmine stain showed positive for Cryptococcal species.

DISCUSSION

Cryptococcosis is a potentially life-threatening fungal infection caused by pathogenic, encapsulated yeasts named Cryptococcus.[1] Among the leading opportunistic infections worldwide, Cryptococcus species contribute significantly to morbidity and mortality in HIV-infected individuals globally, alongside M. tuberculosis and hepatitis viruses.[4] Cryptococcal infection typically occurs by inhalation of spores from environmental reservoirs and subsequent deposition inside pulmonary alveoli, which are normally cleared by the immune system. However, the host's defense to these organisms relies heavily on helper T cell response with cytokine production – mechanisms are severely impaired in HIV-infected patients, leading to uncontrolled fungal proliferation and systemic dissemination.[1]

While cryptococcal meningitis and pneumonia are recognized as the most common clinical manifestations of cryptococcosis in immunocompromised individuals, oral lesions are exceedingly rare. In the context of oral manifestations among HIV-infected patients, conditions such as Kaposi's sarcoma, oral candidiasis, and hairy leukoplakia are far more prevalent and are often considered as clinical indicators of HIV infection.[5] Consequently, the papillary-like mass observed on this patient's tongue warranted consideration of a malignant process in the differential diagnosis.

The clinical diagnosis of cryptococcosis is typically established through the isolation of Cryptococcus species from clinical specimens or by direct visualization using India ink staining of body fluids.[1] In a meta-analysis by E. Temfack et al., detection of the cryptococcal polysaccharide capsular antigen (CrAg) in serum and cerebrospinal fluid (CSF) has garnered increasing attention due to its high diagnostic performance. Reported sensitivities and specificities were 99.7% and 94.1% in serum, and 98.8% and 99.3% in CSF, respectively.[6] Moreover, detection of CrAg has emerged as a valuable tool for early diagnosis of cryptococcal disease, with a median of 22 days before the onset of clinical symptoms.[7] Histopathologically, microscopic examination reveals thickly encapsulated, thin-walled, narrow-budding yeast forms of variable size on hematoxylin and eosin (H&E) staining. Immunohistochemistry plays a crucial role in both diagnosis and differential diagnosis. As with other fungi, Cryptococcus stains positively with Grocott methenamine silver (GMS) and periodic acid–Schiff (PAS)in which demonstrates numerous round to oval intracellular yeasts of varying size. On PAS staining, cryptococcal cell walls appear magenta with a weakly positive or clear capsule. In contrast, GMS staining highlights the organisms as black with a surrounding clear halo against a green background. Notably, mucicarmine is uniquely specific to Cryptococcus species, staining the gelatinous capsule positively and serving as the most specific histochemical stain for diagnosis.[8]

In our case, even though CSF cytology revealed minimal cellularity, microscopic examination of the lesion revealed oval-to-round yeasts scattered in the dermis against the background of mild inflammatory infiltration. These relatively inconspicuous organisms exhibited a pale central nucleus surrounded by a thick, clear capsule-like structure. In addition, local superficial ulcers and bacterial colonies were observed. No malignant cells were identified, thus raising concern for fungal etiology. GMS and PAS stains showed abundant fungal organisms of variable sizes distributed throughout the lesion, involving both epithelial and subepithelial layers. Mucicarmine subsequently confirmed the presence of Cryptococcus species by highlighting a thickened polysaccharide capsule and thin wall in bright pink.

Treatment for Cryptococcal infection is primarily amphotericin B deoxycholate in combination with flucytosine. This regimen is currently regarded as the most effective, achieving more rapid CSF sterilization and reduction of relapse rate, and being associated with lower mortality.[9] However, due to the rarity of oral manifestations of cryptococcosis, data on the efficacy of antifungal therapy in

such lesions remain limited. Further research is needed to better tailor treatment responses and optimize management strategies in these uncommon presentations.

CONCLUSION

This case underscores the importance of maintaining a broad differential diagnosis when evaluating oral lesions in immunocompromised patients, particularly those with HIV/AIDS.[1] While cryptococcosis is typically associated with pulmonary or central nervous system involvement,1 this report illustrates its potential to manifest atypically as a lingual nodule — a rare and often overlooked presentation.[3]

The rarity of such manifestations can lead to delayed diagnosis or misclassification, emphasizing the value of histopathological confirmation. By documenting this unusual case, we aim to raise clinical awareness and support earlier recognition of oral cryptococcosis,[2] ultimately improving outcomes for vulnerable patients. Continued reporting of similar cases will help refine diagnostic approaches and deepen our understanding of the diverse clinical spectrum of this opportunistic fungal infection.[1]

CONFLICTS OF INTEREST

The authors have no conflict of interest to disclose.

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