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CASE REPORT

A soft tissue lesion on the scalp as a peculiar source of disseminated cryptococcosis

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ABSTRACT

Cryptococcosis is a potentially fatal invasive fungal infection with considerable health challenges. A seemingly immunocompetent middle-aged man with frequent exposure to pigeons and bird excreta presented with headaches, fever, gait instability and diplopia. Two years prior to his presentation, he sustained a blunt head trauma which resulted in sporadic headaches. On examination, a hard scalp nodule measuring approximately 3 x 3 cm was palpable on the topmost part of his head. *Cryptococcus neoformans* was cultured from his cerebrospinal fluid, blood and the biopsied scalp nodule. A diagnosis of disseminated cryptococcosis was made, with the scalp lesion being designated as the primary source of the infection. Following a protracted course of antifungal therapy lasting 10 weeks, the patient was asymptomatic without any neurological deficits when reviewed in the clinic at two months post-discharge.

Keywords: Cryptococcosis; *Cryptococcus neoformans*; cutaneous; immunocompetent; scalp.

INTRODUCTION

Cryptococcus neoformans, one of the causative agents of cryptococcosis, is a globally distributed pathogen that has the dubious distinction of being the top-ranked fungal pathogen in the World Health Organization's Fungal Priority Pathogens List (Zhao *et al*., 2023; Dao *et al*., 2024). It is an encapsulated basidiomycetous yeast that exists in the environment and is present in soil, trees, and the droppings of birds (such as pigeons) (Zhao *et al*., 2023). Humans typically become infected through the inhalation of fungal cells; if the lung's alveolar macrophages fail to contain the fungus, it can migrate to the bloodstream and due to its neurotropic nature, cross the blood-brain barrier to result in cryptococcal meningoencephalitis (Chen *et al*., 2022). Although cryptococcal infections most commonly involve the central nervous system, the yeast can also cause cutaneous cryptococcosis (Zhao *et al*., 2023). We report a case of cutaneous cryptococcosis as the source of cryptococcal meningoencephalitis and cryptococcaemia in an immunocompetent adult.

CASE REPORT

A 51-year-old male had been experiencing fever for the past one month, as well as headaches, gait imbalance and diplopia for at least a week. His wife had also noticed that the patient had become more forgetful and irritable for the past one month. Apart from dyslipidaemia, he had no other significant past medical or surgical history. There was also no recent history of travel out of the country. The patient was an active smoker and worked as an air conditioner technician. Due to the nature of his work, he had frequent exposure to pigeons and bird excreta. He reported a blunt head trauma two years ago when an air conditioner part fell onto his head, although no laceration resulted from this incident. Following this event, the patient started to develop sporadic headaches, necessitating occasional visits to the general practitioner for symptomatic treatment.

On admission, he was afebrile with a body temperature of 36.0°C and was hemodynamically stable with a blood pressure of 138/90 mm Hg and a heart rate of 90 beats/minute. His room air oxygen saturation was 97% with a respiratory rate of 22 breaths/minute. He was confused with a Glasgow Coma Scale score of E4V3M5. Neurological examination revealed a positive Kernig sign with an upgoing Babinski sign suggestive of meningoencephalitis. Respiratory, cardiovascular and abdominal examinations were unremarkable. A non-tender hard scalp nodule measuring ≈ 3 x 3 cm was palpable on the topmost part (vertex) of the head.

Laboratory investigations revealed leukocytosis (15.7 x 10^9 cells/L) with a predominance of neutrophils (85%), a normal haemoglobin (15.2 mg/dL) and a normal platelet count (267 x 10^9 cells/L). His C-reactive protein (CRP) was also normal (0.26 mg/dL). Renal and liver function tests, coagulation profile and blood glucose were within normal limits. A chest X-ray revealed no abnormalities.

Infective screening for HIV, hepatitis B and C, toxoplasmosis as well as syphilis were negative.

A lumbar puncture was then done to exclude meningitis and it revealed an elevated opening pressure of 160 cm H_2O and clear cerebrospinal fluid (CSF). Although the CSF did not contain leukocytes or red blood cells, a Gram stain revealed the presence of encapsulated yeast cells which were also India ink-positive (Figure 1). When subjected to a cryptococcal antigen lateral flow assay (IMMMY, Inc., USA), the CSF had a glucuronoxylomannan (GXM) titre in excess of 1:2560. Cream-colored yeast colonies appeared following its culture on Sabouraud dextrose agar (Figure 1). Matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI Biotyper, Bruker-Daltonics, Bremen, Germany) matched our isolate's mass spectral pattern with that of *C. neoformans* P152 CBS with a score of 2.07. A blood specimen collected on the same day as the CSF also grew *C. neoformans* in the aerobic vial.

Despite the absence of classic immunocompromising conditions, the patient was diagnosed with disseminated cryptococcosis. Intravenous amphotericin B deoxycholate (also known as conventional amphotericin B) at a dose of 0.7 mg per kg body weight (i.e. 50 mg) daily was commenced together with oral flucytosine at a dose of 25 mg per kg body weight (i.e. 1500 mg) 6 hourly. An excisional biopsy of the scalp lesion was performed for histopathological examination and fungal culture. Intraoperatively, a chalky, cheesy material measuring 3 x 3 cm was observed at the vertex (Figure 2). Histopathological examination (HPE) revealed chronic granulomatous inflammation with large clusters of epithelioid histiocytes and multinucleated giant cells engulfing numerous yeast-like fungal bodies, which were positive on periodic acid-Schiff (PAS) staining (Figure 2). No malignant change was apparent. The biopsied tissue was positive for *C. neoformans* following culture on Sabouraud dextrose agar.

It was concluded that the scalp lesion was the primary source of the disseminated cryptococcal infection. The patient was then planned for induction therapy with IV amphotericin B given at a dose of 0.7 mg/kg body weight daily, coupled with 1.5 g of oral flucytosine six hourly. The patient achieved CSF and blood culture clearance after two weeks of antifungal therapy. However, on day 21, due to the development of renal impairment, amphotericin B had to be replaced with oral fluconazole at a dose of 1.2 g daily. He was allowed home after a month of hospitalisation. At an outpatient follow-up two months post discharge, the patient was asymptomatic without any neurological deficits. By this time, he had completed a total of 10 weeks of induction therapy and was transitioned to consolidation therapy with 800 mg of oral fluconazole until his next follow-up.

DISCUSSION

Cryptococcosis is an opportunistic mycosis caused by either *C. neoformans* or *Cryptococcus gattii.* While *C. neoformans* has customarily been observed in individuals living with HIV/AIDS, *C. gattii* has a proclivity to occur in immunocompetent individuals (Dao *et al*., 2024). Thus, it is noteworthy that our patient contracted a *C. neoformans* infection even though he was immunocompetent. He however did have one notable risk factor for *C. neoformans* exposure: the very nature of his occupation as an air-conditioner technician directly exposed him to pigeon droppings. Nevertheless, rather than pulmonary symptoms (such as cough or dyspnoea), our patient experienced headaches, likely attributable to a soft tissue lesion on his scalp that developed after being struck by an air conditioner part. We postulate that the object that hit his head had traces of pigeon droppings and traumatically inoculated his scalp skin with *C. neoformans.* The resultant infection, known as primary cutaneous cryptococcosis (PCC), is considered a very rare form of cryptococcosis (Panza *et al*., 2023).

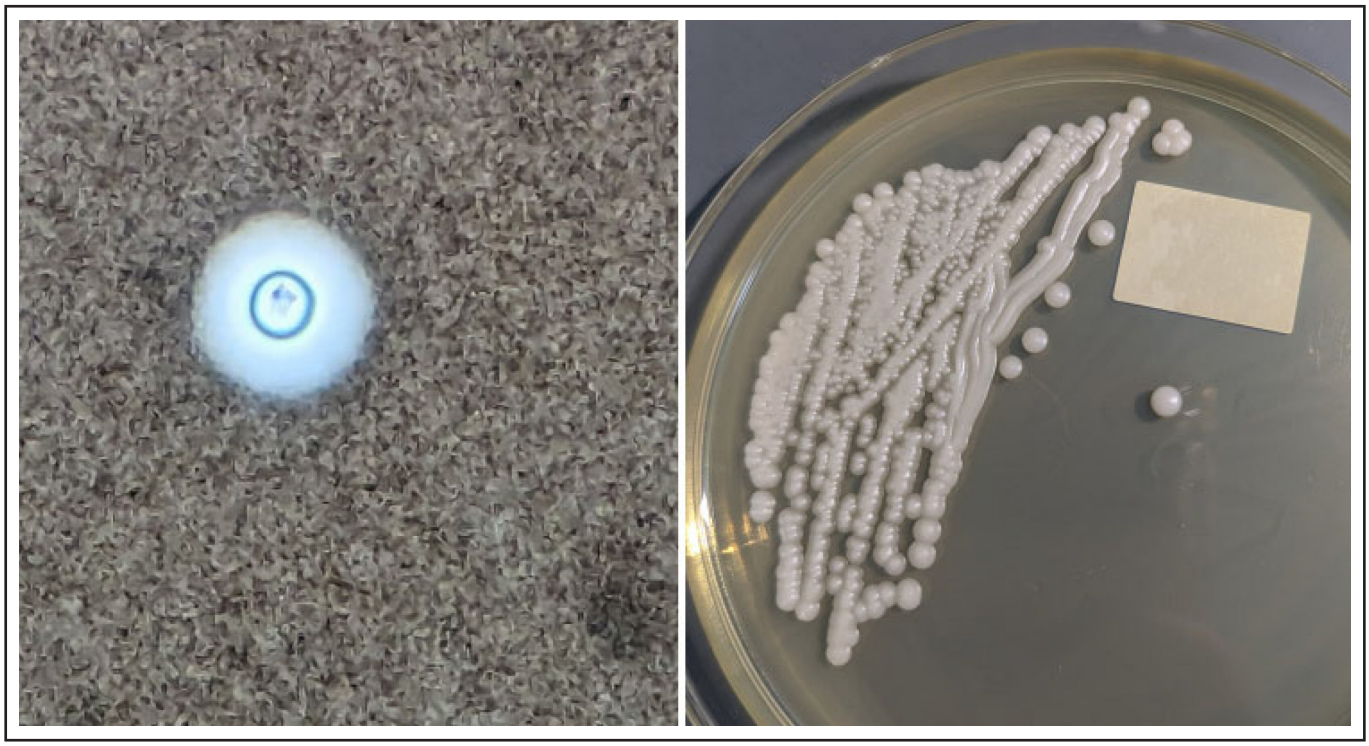

Figure 1. The left image shows a yeast cell surrounded by a clear halo characteristic of *Cryptococcus neoformans* when stained with India ink (x1000 magnification; oil immersion field). The right image shows the moist cream-colored colonies of the yeast when cultured on Sabouraud dextrose agar.

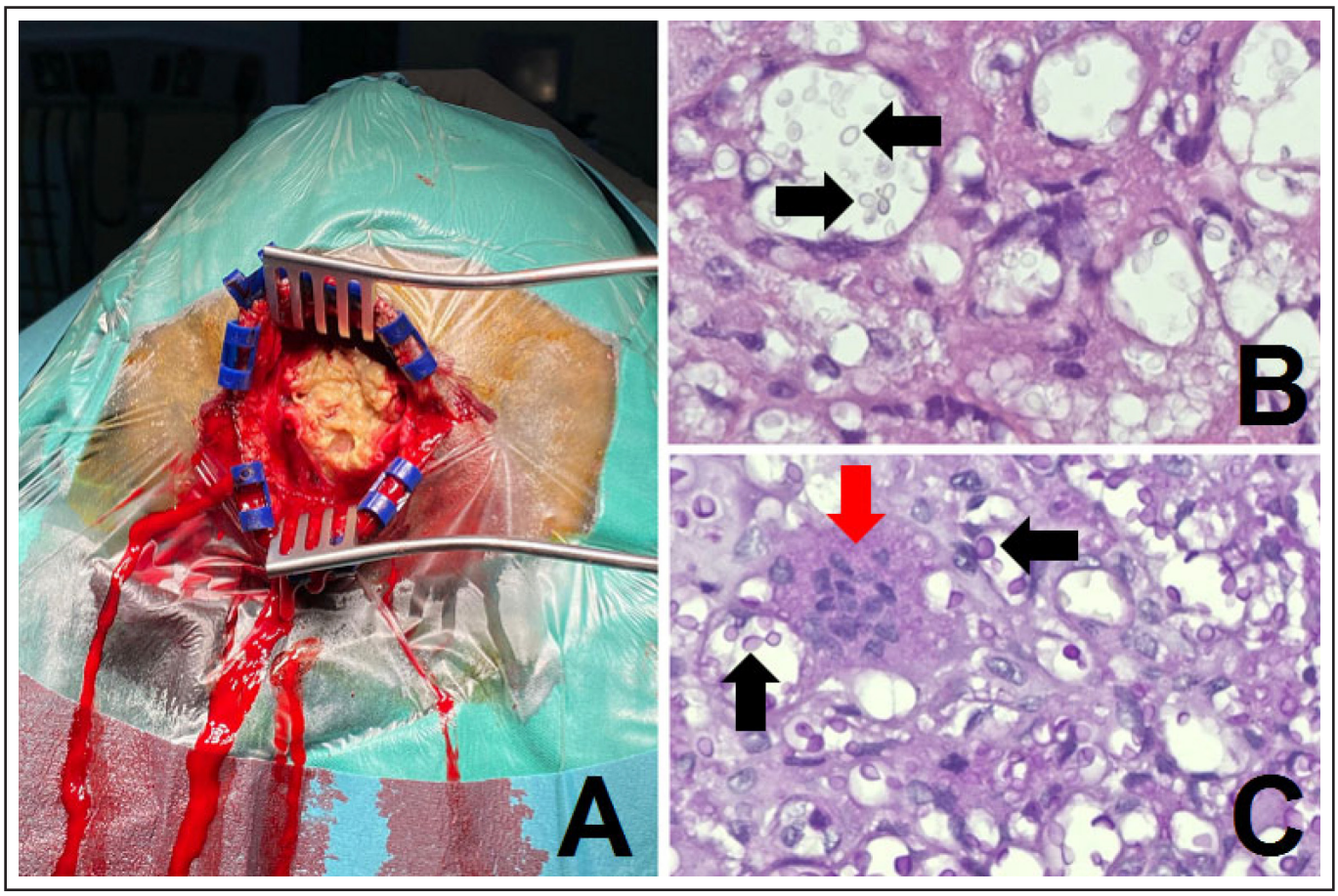

Figure 2. The left image (A) shows the finding of chalky and cheesy material at the vertex during surgery. The right upper image (B) shows the presence of yeast cells (indicated by black arrows) when the biopsied tissue was stained with haematoxylin and eosin (x600 magnification). The right lower image (C) also shows fungal bodies (indicated by black arrows) being highlighted by periodic acid-Schiff staining and a multinucleated giant cell (indicated by a red arrow) (x600 magnification).

Cutaneous cryptococcosis more commonly results from haematogenous dissemination from another site – this is referred to as secondary cutaneous cryptococcosis (SCC) and is seen in up to 20% of cases of disseminated cryptococcosis (Lu *et al*., 2013). Thus, as opposed to PCC, the portal of entry for SCC is the lungs instead of the skin. The very late diagnosis in our patient (i.e. two years after the traumatic incident) is not bewildering because in the medical literature, the duration between symptom onset and PCC diagnosis can range from 1 to 156 weeks (Neuville *et al*., 2003). Even the nature of our patient's cutaneous lesion (i.e. nodular) is not atypical, as PCC lesions can take the form of cellulitis, papules, pustules, plaques, nodules, vesicles, ulcers, or even lesions mimicking those of molluscum contagiosum (Lu *et al*., 2013). Having a solitary lesion further strengthens the notion that our patient had PCC rather than SCC (wherein skin lesions are more likely to be multiple or scattered) (Neuville *et al*., 2003). However, one quaint finding in our case is the lesion's location on the scalp, as PCC tends to involve extremities (particularly the forearm, hands and fingers) (Panza *et al*., 2023).

Owing to its diverse forms or presentation, PCC cannot be reliably diagnosed solely on clinical features. Apart from HPE, fungal culture is also regarded as a gold standard for PCC diagnosis (Chu & Zhou, 2024). The yield of fungal cultures in PCC diagnosis is excellent, with reports of 100% positivity (Neuville *et al*., 2003). Various differential or selective agar media for *C. neoformans* culture have been cited in the medical literature, such as bird seed agar and L-canavanine glycine bromothymol blue agar (CGB). By detecting the production of melanin, bird seed (also known as Niger seed) agar differentiates *C. neoformans* and *C. gattii* from other yeasts (including other cryptococcus species), while the ability to assimilate glycine in CGB agar sets *C. gattii* apart from *C. neoformans* (Klein *et al*., 2009). The use of such specialized agar media may be necessary in centres that rely solely on a biochemical identification kit or platform (such as VITEK 2) for yeast identification because of the inherent inability of biochemical methods to distinguish closely related species (Jin *et al*., 2020). The availability of MALDI-TOF MS somewhat obviates the need for these specialised agar media, as we managed to conclusively identify our *C. neoformans* isolate following culture on just Sabouraud dextrose agar, which is considered the most common and widely used mycological media.

While our patient's skin biopsy did have the typical HPE findings and culture result, both his CSF and blood were also positive for *C. neoformans.* Thus, our patient already had systemic (or disseminated) cryptococcosis at the time of presentation, with the chronology of his symptoms being the fundamental clue to PCC being present initially. If our patient had just PCC, oral fluconazole would have sufficed (Panza *et al*., 2023). However, in the setting of either CNS or disseminated cryptococcosis, the advocated first-line antifungal agents are liposomal amphotericin B plus flucytosine, to be administered as induction therapy for a duration that is retroviral status-dependent (Chang *et al*., 2024). In contrast to HIV-positive individuals who may receive induction therapy for just two weeks, HIV-negative individuals need to be on the same therapy for more than two weeks (Chang *et al*., 2024). We administered conventional amphotericin B to our patient because he was unable to afford liposomal amphotericin B, and his seemingly prolonged induction therapy (i.e. 10 weeks) was due to an interruption in the induction regimen on day 21 (during which fluconazole had to be substituted for amphotericin B).

CONCLUSION

A diagnosis of cryptococcosis must be given due consideration whenever the clinical history unveils significant exposure to pigeons or their droppings. While inhalation of *C. neoformans* is the usual mode of entry of the fungus into the human body, a skin lesion (PCC) can rarely be the initial source of infection, particularly if preceded by a traumatic event. Ruling out disseminated cryptococcosis should then be undertaken, as more aggressive antifungal therapy will be warranted if this is detected.

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Conflict of Interest

The authors declare that they have no conflicts of interest.

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