Cryptococcal Meningitis in an Immunocompetent Man Exposed to a Pet Cockatoo: An Overlooked Zoonosis

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Abstract

Cryptococcus species are commonly isolated in the excreta of birds, but zoonotic transmission has yet to be proven. We report a case of an immunocompetent man with meningitis caused by Cryptococcus neoformans var. grubii with significant exposure to a pet cockatoo highly suspicious for zoonotic transmission. Treatment with intravenous liposomal amphotericin B and oral flucytosine was initiated upon diagnosis, but diagnostic delay because of low suspicion contributed to neurological sequelae. Recognition of pet birds as potential sources of Cryptococcus species' zoonotic transmission is essential for prompt diagnosis and treatment.

Categories: Internal Medicine, Neurology, Infectious Disease
Keywords: pet cockatoo, immunocompetent, cryptococcus neoformans var. grubii, bird, zoonotic transmission, meningitis

Introduction

Cryptococcus species are isolated from bird droppings [1,2], but the potential for zoonotic transmission remains uncertain. Few cases investigate pet birds as a possible source of zoonotic transmission of C. neoformans, most being observed in people with underlying immunodeficiency or malignancy [3-5]. We report a case of C. neoformans var. grubii meningitis in an immunocompetent person with significant exposure to a pet cockatoo supporting zoonotic transmission.

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Case Presentation

A 78-year-old man presented with a one-year history of gait instability that progressed to recurrent falls three weeks before hospitalization. There were no reports of fever, headaches, neck pain, visual changes, dizziness, or modification of his mental status. His medical history included hypertension, deep vein thrombosis, pulmonary embolism, depression, and latent tuberculosis infection (LTBI), for which he was on his eighth month of treatment with isoniazid and pyridoxine. He had a workup initiated by an outpatient neurologist one year ago. MRI brain showed leptomeningeal enhancement. Cerebrospinal fluid (CSF) analysis showed elevated protein and lactate dehydrogenase (LDH), low glucose (Table 1), non-reactive venereal disease research laboratory (VDRL), and negative Mycobacterium tuberculosis complex polymerase chain reaction (PCR) and cultures. CSF cell count and differential were not performed. QuantiFERON®-TB Gold Plus (QIAGEN, Hilden, Germany) was positive. No CSF or serum testing for Cryptococcus or other pathogens was performed. He was referred to the local Department of Public Health for LTBI treatment. Repeated MRI brain after three months showed persistent leptomeningeal enhancement, but no additional workup was obtained. His symptoms worsened over the year, limiting his ability to independently complete activities of daily living.

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### TABLE 1: Cerebrospinal fluid analysis

|                          | Reference Range | Outpatient Lumbar Puncture | Inpatient Lumbar Puncture #1 | Inpatient Lumbar Puncture #2 |
|--------------------------|-----------------|-----------------------------|-----------------------------|-----------------------------|
| Opening pressure         | 10-20 cm H2O    | N/A                         | N/A                         | 13                          |
| Appearance spun          | N/A             | Pale yellow                 | Clear                       |                             |
| Appearance               | N/A             | Hazy                        | Clear                       |                             |
| Red blood cells          | <5 /µL          | N/A                         | N/A                         | 10 (H)                      |
| White blood cells        | <5 /µL          | N/A                         | 285 (H)                     | 112 (H)                     |
| Neutrophils              | 0%              | N/A                         | 23 (H)                      | 8 (H)                       |
| Lymphocytes              | 0%              | N/A                         | 68 (H)                      | 61 (H)                      |
| Macrophages              | 3-37%           | N/A                         | 6                           | 26                          |
| Plasma cells             | %               | N/A                         | 3                           | 5                           |
| Glucose                  | 40-70 mg/dL     | 38 (L)                      | 36 (L)                      | 46                          |
| Protein                  | 12-60 mg/dL     | 464 (H)                     | 284 (H)                     | 198 (H)                     |
| Lactate dehydrogenase    | <=25 U/L        | 44 (H)                      | 55 (H)                      | 26 (H)                      |
| Cryptococcal antigen     | Negative        | N/A                         | 1:320 (H)                   | 1:5 (H)                     |

Examination revealed an overweight man in mild distress with a temperature of 36.9°C, a pulse of 86 beats/minute, a blood pressure of 192/83 mmHg, and a respiratory rate of 17 breaths/minute. He had diminished strength in the lower extremities with significant spasticity, full strength in the upper extremities, and an intention tremor of the right upper extremity. No meningeal signs were found. Cranial nerves, reflexes, sensation, and orientation were intact. MRI brain with contrast revealed bifrontal/bitemporal predominant smooth pachymeningeal enhancement with nodularity along the left frontal convexity dura with a broad-based 7 mm nodule and leptomeningeal enhancement along the basal cisterns, predominantly prepontine and premedullary cisterns (Figure 1). HIV screening was negative. CSF analysis showed elevated white blood cell count with lymphocyte predominance, elevated protein and LDH, and low glucose (Table 1). CSF cryptococcal antigen (CrAg) was positive. Cryptococcus was also detected in BioFire (BioFire Diagnostics, Utah, United States). Within 72 hours, a yeast grew in both Sabouraud Dextrose and brain heart infusion agar, later identified as *C. neoformans var. grubii* by matrix-assisted laser desorption/ionization-time of flight (MALDI-TOF) mass spectrometry (MS) with a log (score) value of 2.25. CSF urease test was positive (Figure 2). Serum CrAg and fungal blood culture were negative.
Infectious diseases (ID) consultation was requested upon diagnosis. During the ID evaluation, the patient denied a prior diagnosis of immunodeficiency, opportunistic infection, past hospitalizations due to an infectious process, or the use of immunosuppressive drugs. He also denied a family history of immunodeficiencies or a recent travel to a tropical or subtropical region. Further questioning revealed that he cared for a pet cockatoo caged indoors for about 10 years. He spent most of the day with the bird, kissed her, fed her, cleaned after her, and on multiple occasions, the bird defecated on him. The cockatoo developed an unknown illness characterized by bloody excreta and feather loss passing away a few months before the patient’s onset of symptoms. Otherwise, he had no exposure to other birds, soil, job hazards, or sick contacts. Given HIV seronegative status, immunodeficiency and malignancy workup were obtained but did not yield significant findings.

The patient was started on induction liposomal amphotericin B and flucytosine. Induction therapy was complicated by acute kidney injury, managed with hydration and correction of electrolyte derangements. In the third week of treatment, a repeated lumbar puncture showed normal opening pressure, reduced white blood cell count, persistent lymphocyte predominance, reduced protein level, normal glucose level, and decreased LDH. CSF CRAg was positive with a lower titer (Table 1). CSF culture was negative. During this time, he had improvement in lower extremity spasticity and right upper extremity tremor, but gait instability persisted. After four weeks, he was transitioned to consolidation therapy with high-dose fluconazole (800 mg daily) with a tentative duration of eight weeks. Maintenance therapy with low-dose fluconazole (200 mg daily) is anticipated for six to 12 months.

**Discussion**
Zoonotic transmission of *Cryptococcus* species has been suspected, given a strong association of *Cryptococcus* with birds, but limited evidence exists. Furthermore, the risk associated with exposure to pet birds is unclear. Few preceding case reports demonstrate associations between pet birds and cryptococcal infections of those exposed [3-6]. Only one case report, in 2005, reported such findings in an immunocompetent patient and was supported by isolation of the same *Cryptococcus* species in the pet bird excreta by molecular testing as that causing infection in the patient [6]. A case report in 2000 also isolated the same species in pet bird excreta by molecular testing as that infecting an immunocompromised patient [3]. In both case reports, neither the immunocompetent patient nor the immunocompromised patient was in physical contact with the pet bird or its excreta [3,6]. In contrast, our patient had direct repeated daily exposure to the excreta of his pet cockatoo and potential aerosolized particles in the presence of the indoor birdcage [7,8]. Furthermore, he was exposed for 10 years in comparison to seven years and three months in the 2000 and 2005 cases reports, respectively [5,6]. This suggests that the patient had prolonged exposure to potentially acquire the infection from his pet bird in the absence of other exposures.

Cryptococcal meningitis was not considered during the initial workup, given the patient’s immunocompetent status despite a year-long history of neurological symptoms. HIV seronegative status further reduced suspicion of cryptococcal infection. Immunocompetent people with cryptococcal meningitis have a delay in diagnosis due to low suspicion of cryptococcal infection [9-12]. Such delay may be attributed to premature closure and failure to recognize atypical presentations of cryptococcal meningitis [9,12]. It was only when CSF CrAg was positive, followed by fungal growth, that the diagnosis was obtained, highlighting the importance of CrAg testing in those presenting with lymphocytic meningitis. If travel history is reported, tropical infections should also be considered. Keeping a broad differential plays a critical role in obtaining an earlier diagnosis. Consequently, the patient was not started on appropriate treatment until over a year after the onset of symptoms.

In addition to his immunocompetent status, his nonspecific presentation may have also contributed to a delay in diagnosis. Compared to immunodeficient people, immunocompetent people who acquire cryptococcal meningitis are less likely to be febrile or have a headache [11-13]. Furthermore, people with known immunodeficiencies are more likely to have an earlier evaluation by ID consultants than immunocompetent people [12]. Delay in ID evaluation has been associated with increased mortality in people with cryptococcal infection [12,14].

When comparing neurological outcomes between immunocompromised and immunocompetent groups with cryptococcal meningitis, the latter group showed higher mortality and more significant neurological sequelae [10-13]. This is thought to be related to diagnostic delays and paradoxical worsening attributed to an intact immune system [15]. Although the patient improved based on repeated CSF analysis and reduction in lower extremity spasticity, he remained at high risk of falls due to persistent gait instability.

**Conclusions**

Cryptococcal meningitis has an atypical presentation in immunocompetent people, which poses a challenge in diagnosis. Furthermore, pet bird exposure is often overlooked as a source of cryptococcal infection. Higher suspicion of cryptococcal infection in the setting of nonspecific symptoms and known pet bird exposure may lead to an earlier diagnosis and, therefore, earlier treatment, potentially reducing neurological sequelae.

**Additional Information**

**Disclosures**

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**References**

1. Anacona C, González C FE, Vásquez-A LR, et al.: First isolation and molecular characterization of *Cryptococcus neoformans* var. *grubi* in excreta of birds in the urban perimeter of the Municipality of Popayán, Colombia. Rev Iberoam Micol. 2018, 35:123-9. 10.1016/j.riam.2018.01.005
2. Litvintseva AP, Kestenbaum L, Vilgays R, et al.: Comparative analysis of environmental and clinical populations of *Cryptococcus neoformans*. J Clin Microbiol. 2005, 43:556-64. 10.1128/JCM.43.2.556-564.2005
3. Nosanchuk JD, Shoham S, Fries BC, et al.: Evidence of zoonotic transmission of *Cryptococcus neoformans* from a pet cockatoo to an immunocompromised patient. Ann Intern Med. 2000, 152:205-8. 10.7326/0003-4819-152-3-200002010-00008
4. Shrestha RK, Stoller JK, Honari G, et al.: Pneumonia due to *Cryptococcus neoformans* in a patient receiving infliximab: possible zoonotic transmission from a pet cockatoo. Respir Care. 2004, 49:606-8.
5. Wegener HH, Staib F: Fatal cryptococcosis in a bird fancier. A clinical case report on pathology, diagnosis and epidemiology of cryptococcosis (Article in German). Zentralbl Bakteriol Mikrobiol Hyg A. 1983, 256:251-8.

6. Lagrou K, Van Eldere J, Keuleers S, et al.: Zoonotic transmission of Cryptococcus neoformans from a magpie to an immunocompetent patient. J Intern Med. 2005, 257:585-8. 10.1111/j.1365-2796.2005.01466.x

7. Ruiz A, Bulmer GS: Particle size of airborne Cryptococcus neoformans in a tower. Appl Environ Microbiol. 1981, 41:1225-9. 10.1128/aem.41.5.1225-1229.1981

8. Staib F: Sampling and isolation of Cryptococcus neoformans from indoor air with the aid of the Reuter Centrifugal Sampler (RCS) and guizotia abyssinica creatinine agar. A contribution to the mycological-epidemiological control of Cr. neoformans in the fecal matter of caged birds. Zentralbl Bakteriol Mikrobiol Hyg B. 1985, 180:567-75.

9. Deming M, Mark A, Nyemba V, et al.: Cognitive biases and knowledge deficits leading to delayed recognition of cryptococcal meningitis. IDCases. 2019, 18:e00588. 10.1016/j.idcr.2019.e00588

10. Brizendine KD, Baddley JW, Pappas PG: Predictors of mortality and differences in clinical features among patients with cryptococcosis according to immune status. PLoS One. 2015, 8:e00451. 10.1371/journal.pone.0000451

11. Bratton EW, El Husseini N, Chastain CA, et al.: Comparison and temporal trends of three groups with cryptococcosis: HIV-infected, solid organ transplant, and HIV-negative/non-transplant. PLoS One. 2012, 7:e43582. 10.1371/journal.pone.0043582

12. Yoon HA, Felsen U, Wang T, et al.: Cryptococcus neoformans infection in human immunodeficiency virus (HIV)-infected and HIV-uninfected patients at an inner-city tertiary care hospital in the Bronx. Med Mycol. 2020, 58:434-45. 10.1093/mmy/myz082

13. Nguyen MH, Husain S, Clancy CJ, et al.: Outcomes of central nervous system cryptococcosis vary with host immune function: results from a multi-center, prospective study. J Infect. 2010, 61:419-26. 10.1016/j.jinf.2010.08.004

14. Hamandi B, Husain S, Humar A, et al.: Impact of infectious disease consultation on the clinical and economic outcomes of solid organ transplant recipients admitted for infectious complications. Clin Infect Dis. 2014, 59:1074-82. 10.1093/cid/ciu522

15. Panackal AA, Wuest SC, Lin YC, et al.: Paradoxical immune responses in non-HIV cryptococcal meningitis. PLoS Pathog. 2015, 11:e1004884. 10.1371/journal.ppat.1004884