A Case of Central Nervous System Cryptococcosis

Jake Gibbons, MD*

Department of Radiology, Baylor University Medical Center, Dallas, USA

***Correspondence:** Jake Gibbons, MD, Department of Radiology, Baylor University Medical Center, 347 Classen Drive, Dallas, Texas 75218, USA

jakegibbons07@gmail.com

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ABSTRACT

Cryptococcal infection of the central nervous system (CNS) has become an increasingly uncommon diagnosis in the advent of antiretroviral therapy for human immunodeficiency virus (HIV). However, patients that are non-compliant with their medications in addition to those who are immunosuppressed outside the realm of HIV remain at risk for this infection. In patients with HIV, those with a CD4 count less than 100 cells per microliter are at particularly high risk for this infection. If not promptly diagnosed and treated with antifungal therapy, CNS cryptococcosis is rapidly fatal. We present a case of a 41-year-old woman with no known medical history that presented to our institution with altered mental status and was ultimately diagnosed with CNS cryptococcosis.

CASE REPORT

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History & Clinical Data

A 41-year-old woman with no known medical history presented to the emergency department with altered mental status. She was found down by a bystander and brought in by ambulance. She was obtunded on arrival to the emergency department and was therefore unable to provide a medical history.

She was afebrile however both tachycardic (134 beats/minute) and tachypneic (18 respirations/minute) on presentation. The patient localized to pain with the sternal rub maneuver. She had scattered skin abrasions. Auscultation of her lungs revealed bibasilar rales.

She was mildly anemic with a hemoglobin of 8.8 g/dL (normal 12.0-16.0 g/dL) and had a normal white blood cell and platelet count. Her creatinine and liver enzymes were within normal limits. She was found to be HIV positive with a viral load of 332,000 copies/mL and an undetectable absolute CD4 count.

Imaging Findings

Non-contrast head CT demonstrated no hemorrhage, acute cortical infarct, mass or mass effect. There were very subtle, ill-defined hypodensities involving the basal ganglia that were indeterminate but thought to potentially reflect dilated perivascular spaces or perforator infarctions. MRI of the brain without and with contrast was performed for further evaluation. This showed innumerable cystic lesions scattered throughout the cerebellum, hemispheric white matter, basal ganglia and midbrain. The cystic lesions were non-enhancing and each measured approximately 1 cm or less in greatest dimension. No additional significant findings were seen within the brain.

Management & Follow-up

In light of the patient's medical history, these findings were suspicious CNS cryptococcosis. A lumbar puncture was performed with CSF cultures growing *Cryptococcus neoformans,* confirming the diagnosis. The infectious disease service was consulted. The patient was started on an aggressive antimicrobial regimen of amphotericin and flucytosine. Despite these measures, the patient remained severely encephalopathic in the setting of fulminant fungal meningoencephalitis. Her clinical status continued to decline and after 45 days in the hospital the decision was made by her family to transition to hospice care.

DISCUSSION

Etiology & Demographics

Cryptococcus neoformans is a ubiquitous fungus that is found predominantly within soil contaminated by bird droppings [1]. It is the most common fungus to infect the CNS and ranks behind only Toxoplasmosis and HIV as a cause for CNS infection in patients with acquired immunodeficiency syndrome (AIDS) [2]. Patients with AIDS are at the highest risk for CNS cryptococcosis when the CD4 count falls below 100 cells/microliter [3]. In the United States, the reported incidence of systemic cryptococcal infection is 0.4-1.3 cases per 100,000 people with a case fatality rate of 12% [2]. The cryptococcal pathogen gains access to the central nervous hematogenously by first infecting the lungs; reactivation of a previously latent

organism is an additional cause for infection [4]. In the advent of antiretroviral therapy, the incidence of cryptococcal infection of the CNS has been reduced considerably [1].

Clinical & Imaging Findings

The clinical presentation of cryptococcal CNS infection is non-specific. Patients often present with altered mental status, as was seen in our patient, and potentially with other signs of meningitis or encephalitis such as fever, seizures, and neck stiffness. Diagnosis can be confirmed through lumbar puncture and identification of the capsular polysaccharide antigen in the cerebrospinal fluid [1].

Cryptococcal infection of the CNS may manifest in several different ways. The organism classically invades the perivascular spaces, which become dilated, forming what are classically described as "gelatinous pseudocysts" [5]. The organisms can also amalgamate to form a granulomatous parenchymal mass, termed a "cryptococcoma" [1]. Finally, the pathogen can cause a generalized meningoencephalitis [5].

The radiologic manifestations of cryptococcus infection of the CNS are variable. Early in the clinical course, imaging of the brain may be entirely normal [5]. Therefore, a high-clinical suspicion is essential in making a prompt and accurate diagnosis. The most common imaging finding, albeit non-specific, is hydrocephalus [6]. "Gelatinous pseudocysts" manifest as dilated cystic spaces within the brain, often described as "soap-bubble" in appearance, most commonly present within the basal ganglia and posterior fossa [1]. Cryptococcomas, or parenchymal granulomas, behave as mass lesions, causing both mass effect and vasogenic edema. Meningitis secondary to cryptococcus is characterized by multifocal meningeal enhancement.

Treatment & Prognosis

If untreated, cryptococcal infection of the CNS is rapidly fatal. Antifungal therapy, typically with agents such as amphotericin B and fluconazole, is the mainstay of treatment. Even with appropriate treatment, there is an estimated mortality rate of 10% to as high as 30% [1]. In patients that survive the primary infection, commonly reported long-term sequelae include dementia, seizures, hydrocephalus and permanent motor or sensory deficits [1].

Differential Diagnosis

The differential diagnosis of CNS cryptococcosis includes viral or bacterial meningitis, progressive multifocal leukoencephalopathy, toxoplasmosis, HIV encephalopathy, and nocardiosis. The imaging findings of 'gelatinous pseudocysts' are a specific manifestation of CNS cryptococcosis. Thus, once these were identified in our patient, the diagnosis became more apparent.

TEACHING POINTS

Cryptococcosis is the most common fungal organism to infect the central nervous system. Imaging manifestations include meningoencephalitis, 'gelatinous pseudocyst' formation, and/or an intraparenchymal cryptococcoma with associated mass effect and edema.

QUESTIONS

QUESTION 1: In addition to gelatinous pseudocysts, which of the following are other potential imaging manifestations of CNS cryptococcosis?

Meningoencephalitis (**applies**)
Hydrocephalus (**applies**)
Vasculitis
Acute infarction
Parenchymal mass with edema (**applies**)

Explanation: Meningoencephalitis, hydrocephalus and parenchymal mass (cryptococcoma) are all potential imaging findings of CNS cryptococcus infection. Hydrocephalus is the most common imaging manifestation [6]. Acute infarction and vasculitis are not usual findings.

QUESTION 2: Which of the following are risk factors for cryptococcal infection of the central nervous system?

1. Male gender
2. Young age
3. HIV (**applies**)
4. Chronic steroid use (**applies**)
5. Female gender

Explanation: Immunosuppression, such as in HIV or chronic steroid use, is the main risk factor for CNS cryptococcosis. There is otherwise not an age or gender predilection.

QUESTION 3: What are the imaging findings of meningitis?

1. T2/FLAIR sulcal hyperintensity (**applies**)
2. Meningeal enhancement (**applies**)
3. Parenchymal hematoma
4. Subdural hemorrhage
5. Sulcal hemosiderin deposition

Explanation: Imaging findings of meningitis include sulcal T2/FLAIR hyperintensity and meningeal enhancement. Both of these findings suggest inflammation within the subarachnoid space such as that seen in meningitis. Parenchymal hematoma, subdural hemorrhage and sulcal hemosiderin deposition are not specific imaging manifestations of meningitis.

QUESTION 4: How does the cryptococcal organism typically infect the central nervous system?

1. Through the gastrointestinal tract
2. Direct spread from soft tissue infection
3. Inhalation into the lungs with hematogenous dissemination (**applies**)
4. Intravenous injection
5. Via the cribriform plate following nasal inhalation

Explanation: The fungal organism is commonly found in bird droppings. It is inhaled into the lungs, where it then enters the bloodstream and spreads to the central nervous system. The other listed answer choices are not typical means by which patients are infected.

QUESTION 5: Which of the following are long-term sequela of cryptococcal infection of the central nervous system?

1. Hydrocephalus (**applies**)
2. Sensory deficits (**applies**)
3. Seizures (**applies**)
4. Dementia (**applies**)
5. Motor deficits (**applies**)

Explanation: Hydrocephalus, sensory and motor deficits, seizures, and dementia are all commonly reported long-term sequela of CNS cryptococcosis [1].

AUTHORS' CONTRIBUTIONS

Gibbons- manuscript preparation, drafting, editing and submission

ACKNOWLEDGEMENTS

None

DISCLOSURES

None

CONSENT

Informed consent was obtained from the patient's medical decision maker. The patient did not have decision making capacity.

HUMAN AND ANIMAL RIGHTS

Not applicable

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FIGURES

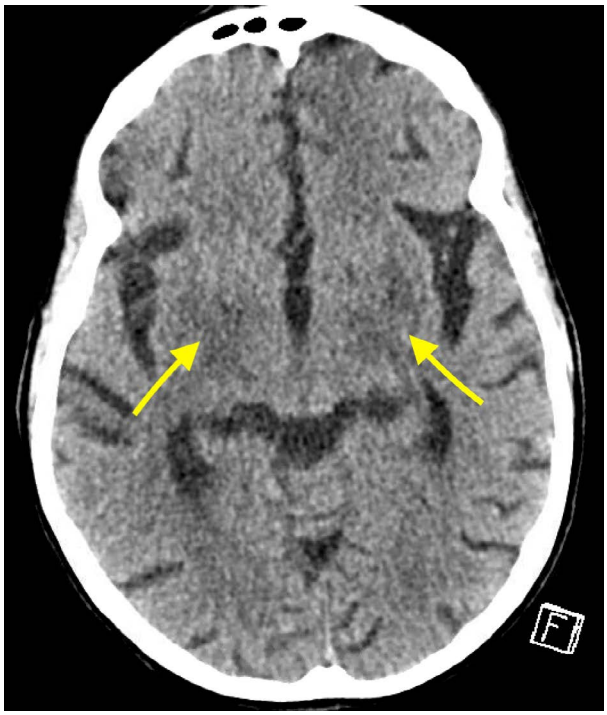

Figure 1: 41-year old woman with CNS cryptococcosis.
FINDINGS: Axial CT of the brain without contrast demonstrates ill-defined hypodensities (arrows) of the bilateral basal ganglia.
TECHNIQUE: Axial CT of the brain without contrast, 200 mAs, 120 kVp, 3 mm slice thickness.

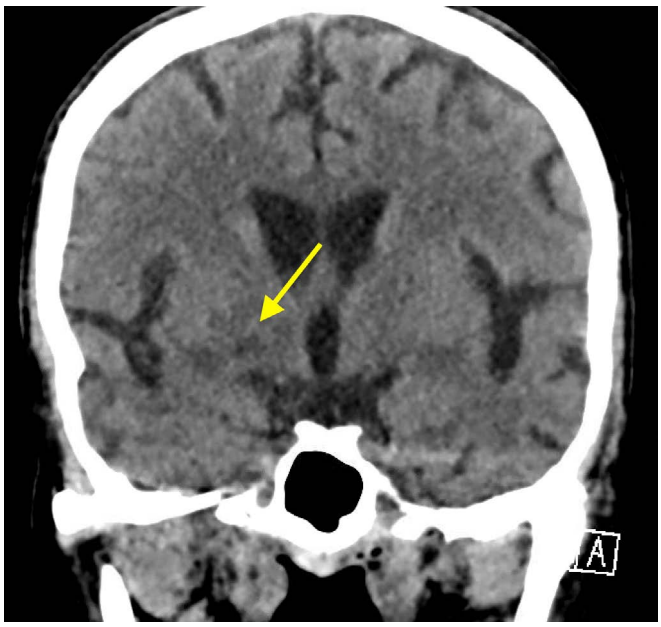

Figure 2: 41-year old woman with CNS cryptococcosis.
FINDINGS: Coronal CT of the brain without contrast demonstrates ill-defined hypodensity (arrow) of the right basal ganglia.
TECHNIQUE: Coronal reconstruction, 200 mAs, 120 kVp, 3 mm slice thickness.

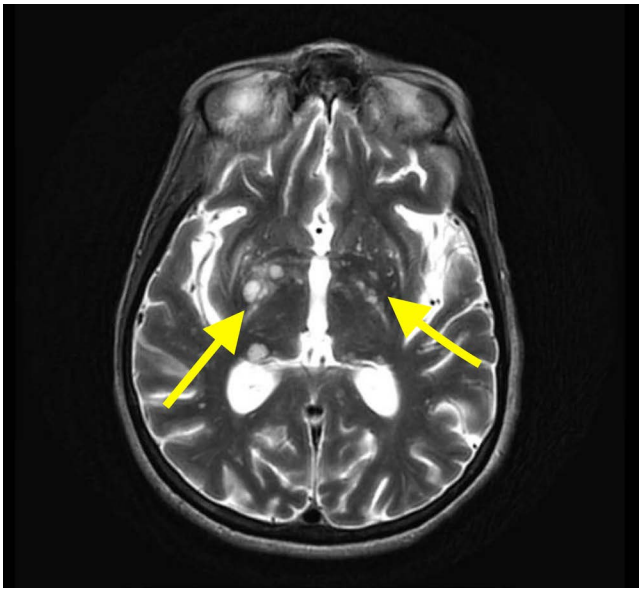

Figure 3: 41-year old woman with CNS cryptococcosis.
FINDINGS: Axial T2 of the brain demonstrates cystic lesions (arrows) of the bilateral basal ganglia. **TECHNIQUE:** 3T MRI, T2 spin echo.

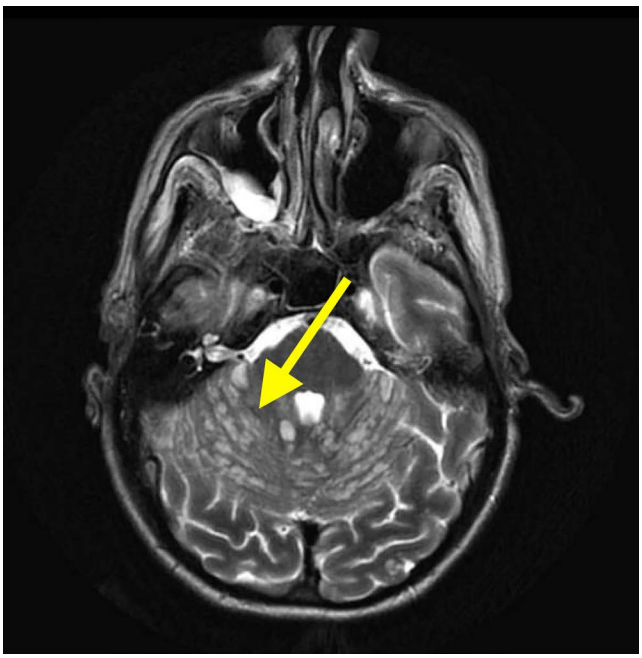

Figure 4: 41-year old woman with CNS cryptococcosis.
FINDINGS: Axial T2 of the brain demonstrates numerous cystic lesions (arrow) of the cerebellum. **TECHNIQUE:** 3T MRI, T2 spin echo.

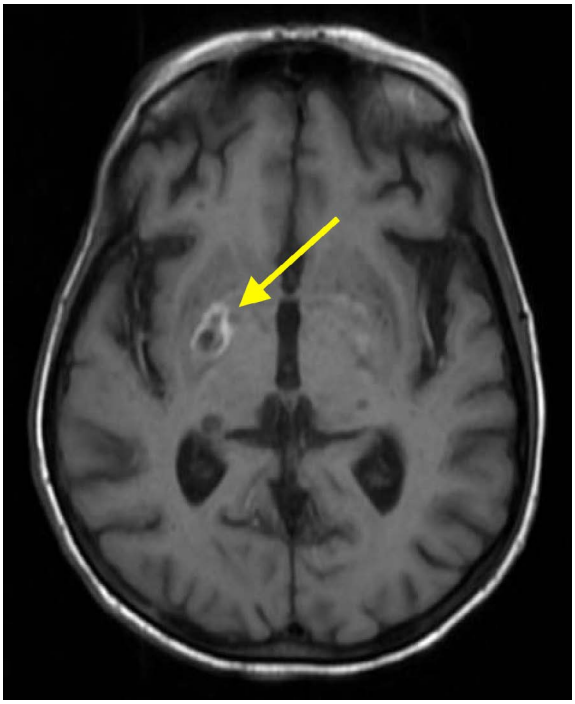

Figure 5: 41-year old woman with CNS cryptococcosis. **FINDINGS:** Axial pre-contrast T1 of the brain demonstrates one of the cystic lesions in the right basal ganglia with a small volume of peri-lesional hemorrhage (arrow).

TECHNIQUE: 3T MRI, T1 spin echo.

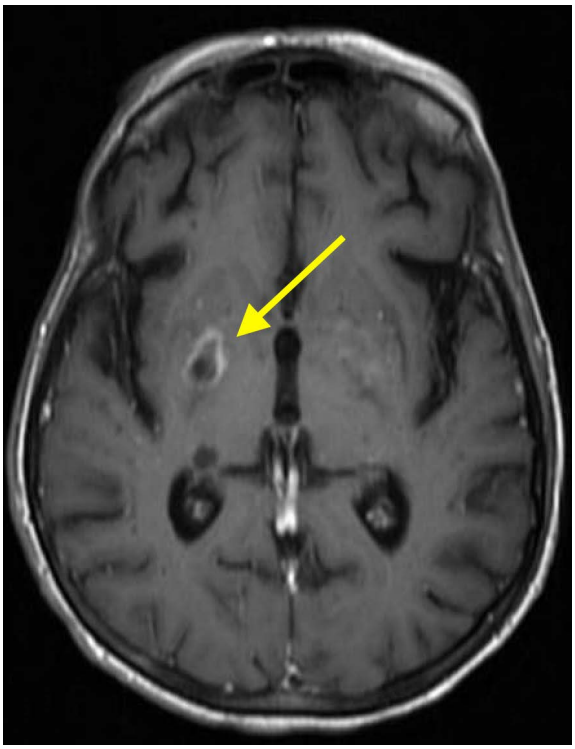

Figure 6: 41-year old woman with CNS cryptococcosis.

FINDINGS: Axial post-contrast T1 of the brain demonstrates no significant enhancement of the prominent right basal ganglia lesion (arrow).

TECHNIQUE: 3T MRI, T1 spin echo post 15 mL Gadolinium intravenous contrast in the venous phase.

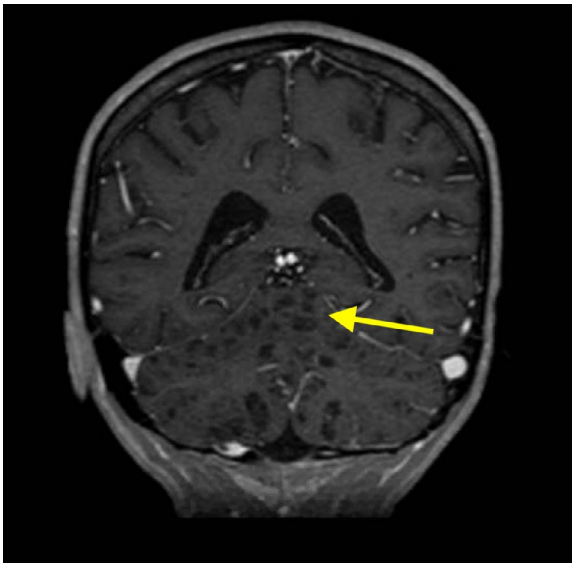

Figure 7: 41-year old woman with CNS cryptococcosis.
FINDINGS: Coronal post-contrast T1 of the brain demonstrates no significant enhancement of the numerous cerebellar lesions (arrow).
TECHNIQUE: 3T MRI, T1 spin echo post 15 mL Gadolinium intravenous contrast in the venous phase.

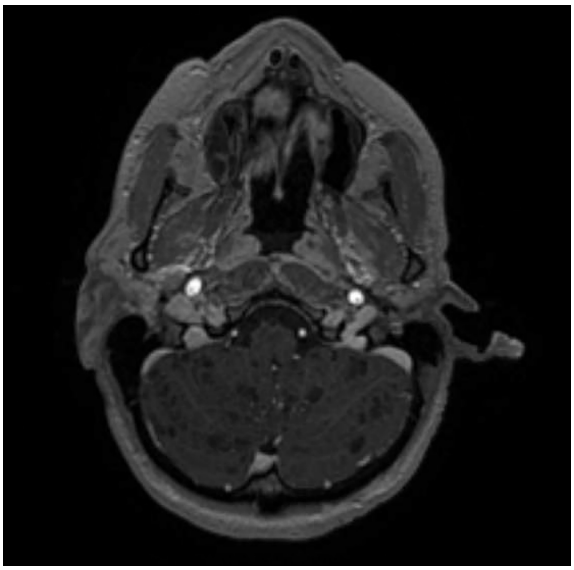

Figure 8: 41-year old woman with CNS cryptococcosis.
FINDINGS: Axial post-contrast T1 of the brain demonstrates no significant enhancement of the numerous cerebellar lesions (arrow).
TECHNIQUE: 3T MRI, T1 spin echo post 15 mL Gadolinium intravenous contrast in the venous phase.

SUMMARY TABLE

Etiology	Inhalation of the fungus with subsequent pulmonary infection. Fungus then spreads hematogenously to the CNS.
Incidence	0.4-1.3 cases per 100,000
Gender Ratio	None
Age Predilection	None
Risk Factors	Immunosuppression, HIV, chronic steroid use
Treatment	Anti-fungal medications such as amphotericin B
Prognosis	Estimated case fatality rate of 12%
Imaging Findings	Non-enhancing cystic lesions (gelatinous pseudocysts) Sulcal T2/FLAIR hyperintensity and meningeal enhancement (meningitis) Cortical expansion, T2/FLAIR hyperintensity +/- cortical enhancement (encephalitis) Enhancing mass lesion with edema and mass effect (cryptococcoma)

KEYWORDS

Cryptococcus neoformans, cryptococcosis, Human immunodeficiency virus, Gelatinous pseudocysts, Meningoencephalitis

ABBREVIATIONS

CNS = CENTRAL NERVOUS SYSTEM
HIV = HUMAN IMMUNODEFICIENCY VIRUS
CT = COMPUTED TOMOGRAPHY
MRI = MAGNETIC RESONANCE IMAGING
CD4 = CD4+ T LYMPHOCYTE CELL
CSF = CEREBROSPINAL FLUID

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