

A Case of Multiple Organ Disseminated Cryptococcosis

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ABSTRACT

Cryptococcus neoformans is an encapsulated yeast found worldwide.¹ Patients with immunosuppression, including individuals with HIV/AIDS, transplant recipients and/or individuals with other T-cell mediated immunosuppression are more susceptible to becoming infected with *Cryptococcus neoformans* than immunocompetent individuals.² This is a case report of a 66-year-old woman who presented to the emergency department with an unsteady gait and urinary incontinence. Magnetic resonance imaging (MRI) on presentation showed a large C5-C6 central disc protrusion. The patient underwent surgical repair and was treated with five days of IV steroids. Later in the course of her hospitalization, she had an unexplained increasing leukocytosis and tachycardia with witnessed episodes of unresponsiveness. She subsequently had a pulseless electrical activity cardiac arrest and succumbed despite resuscitative efforts. A post-mortem diagnosis revealed *Cryptococcus neoformans* fungemia and disseminated cryptococcosis involving multiple organs. Disseminated cryptococcosis primarily affects the central nervous system³, and thus this report presents a rare case of disseminated cryptococcosis involving multiple organs.

KEYWORDS: *Cryptococcus neoformans*, disseminated cryptococcosis, fungal infection, meningoencephalitis

BACKGROUND

Cryptococcus neoformans and *Cryptococcus gattii* are encapsulated yeast arising from the *Cryptococcus* genus and are found throughout the environment. While *Cryptococcus neoformans* is prevalent worldwide, *Cryptococcus gattii* is primarily found in tropical and subtropical areas. *Cryptococcus neoformans* commonly resides in bird droppings, nests and tree bark. Individuals are often infected by *Cryptococcus* through inhalation and infection can occasionally occur through the skin or ingestion.¹ An infection caused by *Cryptococcus neoformans* is classically known as an HIV/AIDS opportunistic infection. Additionally, transplant recipients and/or individuals with other T-cell mediated immunosuppression are susceptible to an infection from *Cryptococcus*

neoformans.² On the other hand, *Cryptococcus gattii* primarily infects immunocompetent individuals.⁴

Individuals are often exposed to *Cryptococcus neoformans* in the environment.⁴ Immunocompetent children living in urban environments have been shown to have positive antibodies to *Cryptococcus neoformans*. This is likely due to frequent environmental exposures.⁵

If infected by *Cryptococcus neoformans*, the yeast often resides in a latent phase or is spontaneously cleared by an immunocompetent host.^{1,4} Both the presence of a latent infection and spontaneous resolution of an infection are likely the cause of positive *Cryptococcus* antibodies in immunocompetent individuals without an obvious preceding cryptococcosis infection. When an individual is infected by *Cryptococcus neoformans*, the clinical presentation can range from an asymptomatic and self-limited pulmonary colonization or infection to disseminated cryptococcosis involving any organ.¹ This is a case report of a patient with a post-mortem diagnosis of multiple organ disseminated cryptococcosis.

CASE REPORT

A 66-year-old woman with a past medical history of type 2 diabetes with retinopathy (recent hemoglobin A1c of 7.7%), hypertension, hyperlipidemia, vitamin B12 deficiency and a left eye pseudomonas corneal ulcer presented to the emergency department with recurrent falls in the setting of a progressive unsteady gait. The patient noted a generalized and unpredictable loss of muscle control with ambulation over the preceding 6–8 months. Her symptoms were not accompanied by dizziness, back pain, focal weakness or numbness. Additionally, she reported a new onset of urinary incontinence. She had recently been referred to a geneticist for evaluation of muscular dystrophy and initial testing was negative.

On presentation to the emergency department, the patient's vital signs were normal. Her physical exam was significant for intact muscle strength in all extremities, decreased sensation in bilateral legs to the knees and a wide-based gait. A non-contrast computed tomography (CT) scan was normal and an MRI of the brain demonstrated scattered small vessel ischemic changes without evidence of an acute infarct, hemorrhage or midline shift. MRI of the entire spine

Figure 1. T2-weighted MRI showing multilevel cervical disc disease



revealed multilevel disc disease in the cervical, thoracic and lumbar spine most pronounced at C5-C6 with a large central disc protrusion (**Figure 1**). Additional work-up on presentation was significant for a white blood cell count of $3.8 \times 10^9/L$ with lymphopenia, a platelet count of $135 \times 10^9/L$, negative treponemal antibodies and normal vitamin B12, folate, and copper levels.

Neurology and Orthopedic Surgery services were consulted and the patient was started on high dose IV dexamethasone for a presumed radiculitis. She underwent an anterior cervical discectomy and fusion of C5-C7 and a C6 corpectomy followed by a posterior C3-T1 fusion. She tolerated the surgical procedures well and there were no operative findings to suggest an infection. IV dexamethasone was continued for a total of five days of treatment. Four days after the second surgical procedure, the patient had a witnessed brief episode of unresponsiveness while ambulating. Tonic-clonic movements were not observed during this episode. Due to an increasing leukocytosis, tachycardia, and an episode of unresponsiveness with behavioral changes, a repeat MRI of the cervical spine with and without IV contrast was obtained looking for a post-operative infection. Postsurgical changes with prevertebral and dorsal paraspinal fluid suggestive of seromas were noted. Additionally, a urinalysis was negative

for an acute urinary tract infection and a chest X-ray showed no acute airspace disease. The patient received fluid resuscitation and was empirically started on ceftriaxone and vancomycin to cover for a surgical site infection as her white blood cell count increased to $27.4 \times 10^9/L$ with a mild increase in a lactic acid level to 2.7 mEq/L. Additionally, she was rescreened for COVID-19 and tested positive after a negative screen three days prior.

The Infectious Disease service was consulted for the increasing leukocytosis and new COVID-19 infection. Antibiotics were subsequently stopped as there was no obvious source of a bacterial infection. Later that day, the patient became hypotensive with a systolic blood pressure in the 80s and with persistent tachycardia. A lactic acid level increased to 6.0 mEq/L. Despite interventions, the patient went into a pulseless electrical activity cardiac arrest without return of spontaneous circulation.

One day after the patient died, the previously collected blood cultures demonstrated budding yeast that later grew *Cryptococcus neoformans*. Autopsy revealed disseminated cryptococcosis involving bilateral lungs, heart, spleen, liver, bilateral kidneys, bilateral adrenal glands, gastrointestinal tract, bone marrow, pancreas, thyroid, bladder, cervix, skeletal muscle and subcarinal lymph nodes. Neuropathology also showed the presence of yeast under a microscopic examination. On autopsy, the patient did not have acute or chronic lung features related to COVID-19. Though her autopsy revealed multiple organ disseminated cryptococcosis, a formal workup for immunosuppression was not completed during the hospitalization as blood cultures did not turn positive for budding yeast until after the patient passed away.

DISCUSSION

This is a case report of a patient who presented to the emergency department with subtle neurologic symptoms and was ultimately found to have multiple organ disseminated cryptococcosis on autopsy. In one study of 65 individuals diagnosed with *Cryptococcus neoformans* fungemia, 18.5% of the patients did not carry an immunosuppressive diagnosis. 11.32% of the 65 patients had diabetes without other known immunosuppressive etiologies as seen with the patient in this case report. Immunosuppressed individuals were more likely to be diagnosed with disseminated cryptococcosis compared to immunocompetent individuals.⁶

Upon dissemination from the respiratory tract, *Cryptococcus neoformans* favors travel to the central nervous system often resulting in a subacute meningoencephalitis. Patients with subacute cryptococcosis meningoencephalitis may present with a fever, headache, altered mental status, stiff neck, nausea and vomiting. Patients can also present with visual symptoms, hearing loss, ataxia, aphasia, seizures and chorea.³ Immunocompetent individuals may present

with indolent cryptococcosis meningoencephalitis and it may take up to 8 months for a diagnosis to become apparent.^{3,7} Additionally, only about 50% of non-HIV patients are febrile.³

The patient's progressive ataxic gait may have been a subtle presentation of a subacute cryptococcosis meningoencephalitis. In addition to the new leukocytosis and tachycardia, she developed personality changes, neck pain (though recently had neck surgery), somnolence and had episodes of unresponsiveness after receiving IV steroids. Since steroids can cause immunosuppression, it is possible that the IV steroids transitioned a subacute subtle meningoencephalitis to sepsis from multiple organ disseminated cryptococcosis. Additionally, the patient had lymphopenia at baseline, which may have been a contributing factor to the disseminated cryptococcosis diagnosis.

There is an increasing incidence and prevalence of fungal infections worldwide. An increase in the number of hematopoietic stem cell transplant recipients and more individuals treated with immune modifying agents have led to an increase in immunosuppressed patients. This patient population is more susceptible to fungi that were previously less prevalent, including *Histoplasma capsulatum* and *Fusarium*.⁸

Diagnosing an invasive fungal infection is difficult.⁹ Patients often present without specific symptoms and histopathology and culture have low sensitivity, leading to diagnostic delay. Recently, techniques have been developed to aid in diagnosing fungal infections, such as the galactomannan antigen test for aspergillosis or the specific antigen and antibody test for detecting the *Cryptococcus* species. Additionally, new molecular methods to rapidly diagnose fungal infections have shown favorable potential, such as polymerase chain reaction (PCR) assays, matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) techniques and fluorescence *in situ* hybridization (FISH) techniques.^{9,10}

Overall, the immune status of the individual with cryptococcosis determines the clinical manifestation. For individuals with cryptococcosis meningitis, immunocompetent individuals are less likely to also have fungemia or extra-neural involvement compared to immunosuppressed individuals. The presence of fungemia in patients with cryptococcosis often results in poor outcomes.⁷ Given that disseminated cryptococcosis is most commonly found in the central nervous system³, this case report presents a rare case of dissemination involving multiple organs. *Cryptococcus neoformans* can infect both immunocompetent and immunosuppressed individuals and a diagnosis is often delayed due to nonspecific symptoms at clinical presentation and the low sensitivity of histopathology and culture.

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