

Cryptococcosis in the Immunocompetent Patient

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Introduction

Cryptococcus gattii, formerly known as *Cryptococcus neoformans var gattii*, is an encapsulated yeast that causes disease in both immunocompetent and immunosuppressed individuals. The organism enters via the respiratory tract and causes a spectrum of illness ranging from asymptomatic infection to severe illness, including pneumonia and disseminated infection involving multiple sites, including the central nervous system, eyes, and skin.

We describe the case of a 25-year-old man without prior medical history who presented with a seizure and was found to have concurrent pulmonary and central-nervous-system mass lesions that were due to cryptococcal infection. This case illustrates the importance of considering infectious causes such as *C. gattii* in the differential diagnosis of mass lesions involving multiple organ systems, regardless of the patient's immune status.

Case Summary

A 25-year-old man presented to the emergency department following a witnessed generalized tonic-clonic seizure that lasted for approximately one minute. He had no prior seizure history but did note 3 episodes of headache over the preceding 7 months, which were accompanied by nausea, photophobia, and right hemianopsia, which ceased

spontaneously after approximately 8 hours. On review of systems, he also noted one episode of syncope, attributed to dehydration, 4 months earlier, as well as new jaw and back pain. He denied fever, chills, weight loss, chest pain, dyspnea, or cough.

He had no significant medical history and was not taking any medications, including over-the-counter medications or herbal supplements. His family history was remarkable for the fact that his mother had hypersensitivity pneumonitis, and 3 paternal aunts had breast cancer. Recently married, he was en route to a cruise in Alaska and had been in Seattle for only 2 days. His wife was his only lifetime sexual partner, and he had no history of intravenous drug or tobacco use. He was born and currently lives in northern California. He had never traveled outside the country and had not been outside his home region in the past year. He worked as a manager in an automobile parts distribution warehouse and did not own any pets, although his mother previously owned 2 parrots.

In the emergency department his vitals included temperature 35.9°C, blood pressure 117/65 mm Hg, heart rate 77 beats/min, respiratory rate 18 breaths/min, and room-air oxygen saturation 100%. He was oriented to person, place, and time, but was drowsy, had latency of speech, and did not recall the events surrounding the seizure. A detailed neurologic examination was otherwise unremarkable, and had no deficits in motor, sensory, cerebellar, or visual function. Oral examination revealed a small laceration on the left lateral tongue. The cardiac, pulmonary, abdominal, and skin examinations were normal, and he had no lymphadenopathy, masses, or organomegaly. He had tenderness to palpation of the paraspinous muscles and latissimus dorsi.

Basic laboratory studies revealed white-blood-cell count of 12.4×10^9 cells/L, with a differential of 5.2 neutrophils, 6.2 lymphocytes, and 0.1 eosinophils. Chemistry studies revealed sodium 136 mg/dL, potassium 5.7 mg/dL, chloride 100 mg/dL, bicarbonate 18 mg/dL, blood urea nitrogen 14 mg/dL, creatinine 1.1 mg/dL, lactate dehydrogenase 529 U/L (normal value < 200 U/L), creatinine kinase 169 U/L (normal), alpha-fetoprotein < 5.0 ng/mL, and beta human chorionic gonadotropin 1 mIU/mL. His

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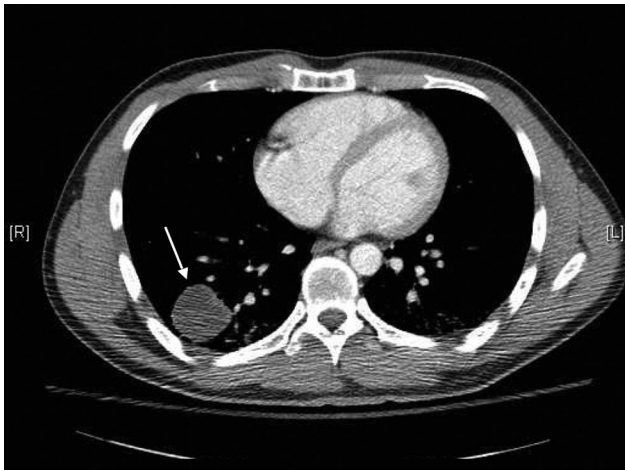


Fig. 1. Non-contrast computed tomogram shows a 3.5×3.6 cm homogeneous non-calcified lung mass in the right lower lobe of the lung (arrow).

blood alcohol level was negative, as were enzyme immunoassays for human immunodeficiency virus (HIV).

Portable chest radiograph revealed a focal, rounded opacity in the infrahilar region of the right lung. Computed tomogram (CT) showed a 3.5×3.6 cm well-circumscribed, homogeneous, non-calcified lung mass in the posterior right lower lobe (Fig. 1). A non-contrast CT of the head showed a large confluent area of vasogenic edema in the left occipito-parietal region, without definite evidence of an underlying mass lesion. Magnetic resonance imaging of the brain later revealed a 3.0×3.3×1.5 cm ring-enhancing heterogeneous cystic lesion in the left parietal lobe, with surrounding vasogenic edema extending into the occipital and posterior left frontal lobe white matter (Fig. 2). Sonogram of the testicles showed no evidence of masses or cystic lesions.

Following admission to the neurology service, he received phenytoin, after which he had no further seizure activity. The pulmonary service was consulted for evaluation of the opacity seen on chest imaging. Flexible bronchoscopy revealed an endobronchial lesion in the lateral basal segment bronchus of the right lower lobe (Fig. 3). Biopsy of that lesion and bronchial wash of the right middle lobe were performed. Cytology of the lavage specimen revealed no malignant cells but did show rounded yeast forms with rare narrow-based budding and a thick capsule. Histopathologic examination of the biopsy specimen revealed granulomatous inflammation with rare encapsulated yeast forms consistent with cryptococcus (Fig. 4).

He was discharged from the hospital prior to release of the final pathology results, and returned to northern California. When the results became available, he was contacted via telephone and advised to go to a local hospital. Following admission, CT-guided biopsy of the lung mass was performed and revealed *Cryptococcus gattii* by growth

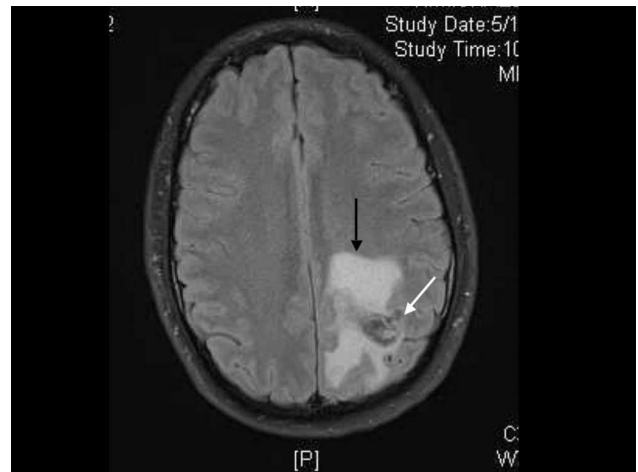


Fig. 2. Single axial flair magnetic resonance image shows a 3.0×3.3×1.5 cm heterogeneous cystic lesion in the left parietal lobe of the brain (white arrow), with surrounding vasogenic edema (black arrow) extending to the occipital lobe.

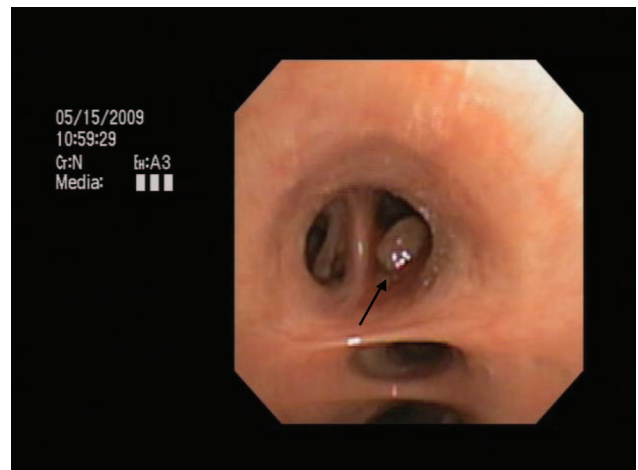


Fig. 3. Bronchoscopic view from the bronchus intermedius shows a non-obstructing endobronchial lesion (arrow) in the lateral basal segmental bronchus of the right lower lobe.

on fungal media and molecular typing. Serum cryptococcal antigen was positive, with a titer of approximately 1:4, whereas cerebrospinal-fluid cryptococcal antigen and culture were negative. Further workup, including T-cell subsets and immunoglobulin levels, found no evidence of immunodeficiency. He was treated with a 6-week induction regimen of amphotericin B and flucytosine, during which time he developed renal insufficiency and anemia. He was ultimately maintained on a prolonged course of consolidation therapy with high-dose fluconazole. Follow-up imaging after 11 months showed a substantial decrease in the size of the brain lesion, with resolution of surrounding cerebral edema (Fig. 5). Follow-up serum cryptococcal antigen titer was negative. His anti-seizure ther-

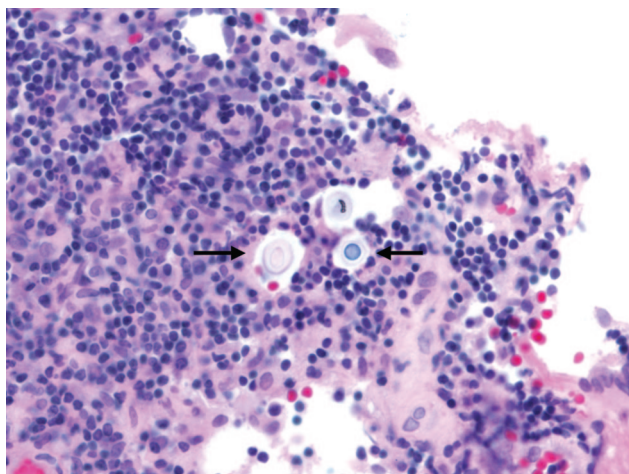


Fig. 4. Hematoxylin and eosin preparation of biopsies from the endobronchial lesion exhibit epithelioid cells and mononuclear-cell infiltrate typical of granulomatous inflammation. The arrows point to the encapsulated yeast forms, which have clear mucopolysaccharide capsules.

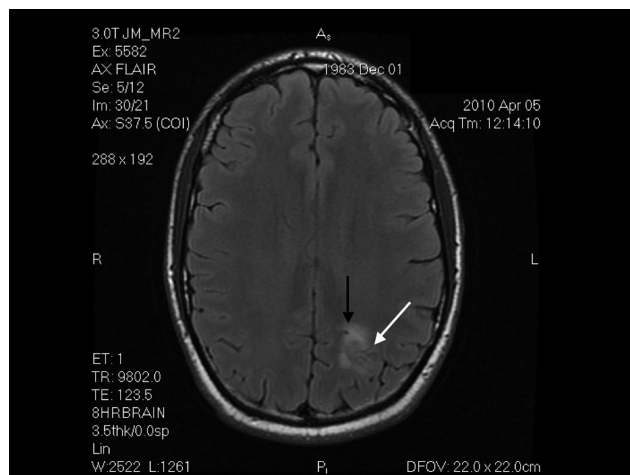


Fig. 5. Single axial flair magnetic resonance image 11 months after original diagnosis shows interval decrease in the size of the brain lesion (white arrow) and surrounding vasogenic edema (black arrow).

apy was changed from phenytoin to levetiracetam. He is currently asymptomatic and has had no further seizure activity.

Discussion

Our patient presented with pulmonary and central-nervous-system masses and was found to have *Cryptococcus*

gattii infection. When faced with the presence of concurrent pulmonary and brain lesions, clinicians must consider malignant and infectious processes as possible etiologies. The differential diagnosis for the malignant processes includes primary lung cancer with brain metastasis, and other metastatic processes such as testicular cancer or melanoma, whereas the differential diagnosis for infectious processes includes bacteria (eg, nocardia); mycobacteria; parasites (eg, toxoplasma); and fungi such as cryptococcus, aspergillus, fusarium, zygomycetes, coccidioides, histoplasma, and pseudoallescheria.

The diagnosis can be made in such cases by sampling from the most readily accessible site. Given the higher risk associated with brain biopsy, this will typically involve obtaining lung specimens for culture, cytology, and histopathology, via bronchoscopy with bronchoalveolar lavage, and, if airway lesions are identified, endobronchial biopsies, CT-guided biopsy with more peripheral lesions, or open-lung biopsy if less invasive means fail to make a diagnosis. Our patient initially underwent bronchoscopy, and the cytology and endobronchial biopsy specimens revealed a cryptococcal infection—a finding later confirmed via CT-guided biopsy of the lung mass.

Cryptococcus is an encapsulated, haploid yeast that causes disease in both immunocompetent and immunosuppressed individuals. The 2 predominant pathogenic strains of the organism, *C. neoformans* and *C. gattii*, are generally found in soil, bird excrement, and in the bark of certain trees, including eucalyptus, fir, and alder.¹ The organism enters the host via inhalation and travels to the respiratory system, where it is either cleared from the host or causes active infection. The yeast grows well at 37°C, with virulence due in part to its mucopolysaccharide capsule, which deters phagocytosis. While *C. neoformans* has a worldwide distribution, *C. gattii* was thought to be predominantly located in tropical and subtropical regions, but a recent outbreak in Vancouver Island, British Columbia, suggested the organism has a wider distribution that includes the Pacific Northwest and Northern California.² Our patient had been in the Pacific Northwest for only 2 days prior to the onset of symptoms, which suggests that he probably acquired his infection in northern California.

Cryptococcosis is more common in immunocompromised patients, including those with impaired cell-mediated immunity, as in HIV, hematologic malignancies, and solid-organ transplant recipients, and patients on chronic corticosteroids or other immunosuppressive therapy.³ Symptomatic disease does occur in immunocompetent hosts, however, as evidenced by the recent case descriptions.^{1,4} *C. neoformans* is the predominant strain in both immunosuppressed and immunocompetent individuals,³ but *C. gattii* is increasingly being recognized as a cause of infection in immunocompetent patients.

Up to one third of infected immunocompetent patients do not manifest symptoms and only come to attention when chest radiographs done for other purposes reveal an abnormality.⁵ The remainder present with a variety of symptoms, including fever, cough, dyspnea, and chest pain. The radiologic manifestations are varied and include solitary or multiple well defined calcified or non-calcified nodules (referred to as cryptococcomas), mass-like opacities, pleural effusions, hilar adenopathy, and cavitary lesions.³ Nodular lesions are the most common of these findings in immunocompetent patients, whereas immunosuppressed patients are more likely to have alveolar or interstitial opacities and evidence of cavitation. Endobronchial lesions, such as the one seen in our patient, are rare and have been described in only 15 prior cases.⁶⁻⁸

In addition to these pulmonary manifestations, cryptococcus may also cause symptomatic disease in other organ systems, including the central nervous system, skin, prostate, and eyes. Central-nervous-system involvement often manifests as meningitis or meningoencephalitis, but can, in some cases, present as isolated cryptococcomas. Dissemination to the central nervous system and other sites is more common in the immunosuppressed, although reports from the Vancouver Island outbreak¹ and Australia⁹ demonstrate that central nervous system involvement occurs in immunocompetent individuals as well.

The diagnosis of pulmonary cryptococcosis can be confirmed with one of several methods. The organism can be isolated from sputum or bronchoalveolar lavage samples, with routine mycologic media. Bronchoalveolar lavage samples can also be tested for cryptococcal antigen; a titer of > 1:8 is highly sensitive for the diagnosis of pulmonary disease in both HIV and non-HIV individuals.¹⁰ Serum cryptococcal antigen titer can be measured in immunocompetent patients with isolated pulmonary disease, but a negative titer does not rule out the diagnosis. A positive titer in that population is highly suggestive of spread to extra-pulmonary sites. Histopathology specimens and bronchoalveolar lavage fluid can be examined with various stains, including India ink, and more specific stains for the capsular polysaccharide, such as mucicarmine, periodic acid Schiff, and alcian blue. When necessary, *C. gatii* can be distinguished from *C. neoformans* with concanavine-glycine thymol blue agar¹¹ monoclonal-antibody testing, and nucleic-acid-amplification techniques. When a diagnosis of pulmonary cryptococcosis is made, central nervous system disease should be excluded with imaging and lumbar puncture if the patient has any central-nervous-system symptoms, positive serum cryptococcal antigen, or risk factors for disseminated disease.

The treatment of cryptococcosis depends on the immune status of the host and the clinical manifestations.¹² Mild to moderate disease limited to the respiratory system is usually treated with fluconazole in both immunocom-

petent and immunosuppressed individuals. Well selected immunocompetent patients may be observed for evidence of spontaneous remission, although recent guidelines suggest treating even those who are asymptomatic.¹² Patients with severe disease, central-nervous-system involvement, or any other evidence of dissemination are treated with an "induction" regimen of amphotericin B and flucytosine followed by "consolidation" fluconazole. Immunocompetent patients are typically treated for 12 months, whereas immunosuppressed individuals remain on lifelong fluconazole, or until their immune impairment resolves or improves.¹²

Our patient presented with seizure and a central-nervous-system mass lesion and was found to have pulmonary cryptococcosis. This case demonstrates the importance of considering cryptococcosis in immunocompetent patients who present with isolated pulmonary nodules or concurrent pulmonary and central-nervous-system mass lesions.

Teaching Points

- Infectious causes, including fungal infections, should be considered on the differential diagnosis of mass lesions involving multiple organ systems.
- Although more common in immunocompromised patients, cryptococcosis can occur in immunocompetent patients and should be considered on the differential diagnosis for nodular or mass-like lesions in such patients.
- Patients diagnosed with pulmonary cryptococcosis should undergo evaluation for neurologic involvement if they have any central-nervous system symptoms, positive serum cryptococcal antigen, or risk factors for disseminated disease such as immunosuppression.
- Appropriate treatment of cryptococcosis will depend on the clinical manifestations and immune status of the affected patient. Recent guidelines suggest treating even those who are asymptomatic with a fluconazole-based regimen, while those patients with more severe or widespread disease will require more aggressive initial therapy with amphotericin and flucytosine.

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REFERENCES

1. Kidd SE, Hagen F, Tscharke RL, Huynh M, Bartlett KH, Fyfe M, et al. A rare genotype of *Cryptococcus gatii* caused the cryptococcosis outbreak on Vancouver Island (British Columbia, Canada). *Proc Natl Acad Sci USA* 2004;101(49):17258-17263.

2. Iqbal N, DeBess EE, Wohrle R, Sun B, Nett RJ, Ahlquist AM, et al. Correlation of genotype and in vitro susceptibilities of *Cryptococcus gattii* strains from the Pacific Northwest of the United States. *J Clin Microbiol* 2010;48(2):539-544.
3. Chayakulkeeree M, Perfect JR. Cryptococcosis. *Infect Dis Clin North Am* 2006;20(3):507-544;v-vi.
4. Datta K, Bartlett KH, Baer R, Byrnes E, Galanis E, Heitman J, et al. Spread of *Cryptococcus gattii* into Pacific Northwest region of the United States. *Emerg Infect Dis* 2009;15(8):1185-1191.
5. Campbell GD. Primary pulmonary cryptococcosis. *Am Rev Respir Dis* 1966;94(2):236-243.
6. Huang CJ, Yang MC, Ueng SH. Large cryptococcoma mimicking lung cancer in an HIV-negative, type 2 diabetic patient. *J Thorac Imaging* 2005;20(2):115-117.
7. Piyavisetpat N, Chaowanapanja P. Radiographic manifestations of pulmonary cryptococcosis. *J Med Assoc Thai* 2005;88(11):1674-1679.
8. Karnak D, Avery RK, Gildea TR, Sahoo D, Mehta AC. Endobronchial fungal disease: an under-recognized entity. *Respiration* 2007;74(1):88-104.
9. Mitchell DH, Sorrell TC, Allworth AM, Heath CH, McGregor AR, Papanoum K, et al. Cryptococcal disease of the CNS in immunocompetent hosts: influence of cryptococcal variety on clinical manifestations and outcome. *Clin Infect Dis* 1995;20(3):611-616.
10. Baughman RP, Rhodes JC, Dohn MN, Henderson H, Frame PT. Detection of cryptococcal antigen in bronchoalveolar lavage fluid: a prospective study of diagnostic utility. *Am Rev Respir Dis* 1992;145(5):1226-1229.
11. Jarvis JN, Harrison TS. Pulmonary cryptococcosis. *Semin Respir Crit Care Med* 2008;29(2):141-150.
12. Perfect JR, Dismukes WE, Dromer F, Goldman DL, Graybill JR, Hamill RJ, et al. Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the Infectious Diseases Society of America. *Clin Infect Dis* 2010;50(3):291-322.