

CLINICAL MYCOLOGY COURSE

CASE 2: A 45-YEAR-OLD MAN WITH A HARD MASS IN HIS THIGH PRESENTED BY JOHN R. PERFECT, MD



Initial Presentation

The patient is a 45-year-old white man living in North Carolina who is taking no medications and has no known apparent underlying disease. He presents with a hard mass in his right thigh, which had been growing for several weeks. The mass is not painful or warm, and the overlying skin is normal. His temperature was normal, and he did not remember any trauma to the thigh. At his initial presentation, he has no respiratory or central nervous system symptoms or signs. His occupation is a medical research technician. His recent travel history was to the San Francisco area about 5 months ago, where he stayed for 3 weeks.

Challenge Question 1. What would be your next diagnostic move?

- A. Percutaneous biopsy of the mass with histopathology and culture
- B. Radiograph of the leg to determine if there is any bone involvement
- C. Empiric treatment of the patient with antibiotics because it is likely to be an abscess
- D. MRI scan of the leg to determine characteristics of the mass
- E. Observe the mass for another 6 weeks to determine if lesion will continue to grow or regress

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Discussion

- A. Percutaneous biopsy of the mass with histopathology and culture.** Eventually, tissue will be necessary to rule out tumor vs infection, but first it would be better to obtain a precise definition of the mass.
- B. Radiograph of the leg to determine bone involvement.** A radiograph (plain film) of the leg would not give enough information regarding the mass and probably does not need to be performed.
- C. Empiric treatment of the patient with antibiotics because it is likely to be an abscess.** The use of empirical antibiotics is not helpful here without defining what the mass is. There is no certainty that this is an abscess. In fact, the patient has no signs of infection, and it could be a neoplasm.
- D. MRI scan of the leg to determine characteristics of the mass.** This mass has grown for approximately 5 months and the present differential diagnosis includes probable tumor with a possible alternative diagnosis of a cold abscess. The best next step for diagnosis is a magnetic resonance imaging (MRI) scan.
- E. Observe the mass for another 6 weeks to determine if lesion will continue to grow or regress.** As malignancy and infection are in the differential diagnosis, there is no reason to delay diagnosis.

Correct answer: D.

Work-up

The MRI scan was performed and showed a 5 x 4 x 4 cm mass within the right thigh (Figure 1). The mass had mild heterogenous enhancement on T2 imaging and some changes consistent with muscle edema around the mass. The MRI picture was consistent with a malignancy. Therefore, the patient had a computed tomography (CT) scan of his chest, abdomen, and pelvis to rule out metastatic disease. Interestingly, the body CT scan revealed a spiculated 2-cm left lower lobe lung mass with multiple bilateral sub-centimeter pulmonary nodules (Figure 2). At this point, it was clear that he needed a tissue diagnosis, so the patient underwent a percutaneous biopsy of the thigh mass.

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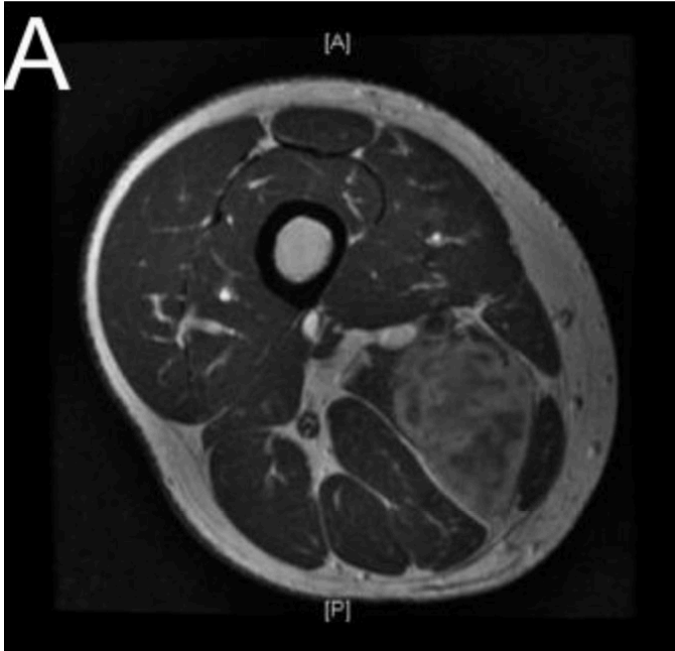


Figure 1. MRI image of the patient's upper thigh mass. Reprinted from Byrnes EJ 3rd, et al. *PLoS One*. 2009,10;4(6):e5851. doi: 10.1371/journal.pone.0005851.

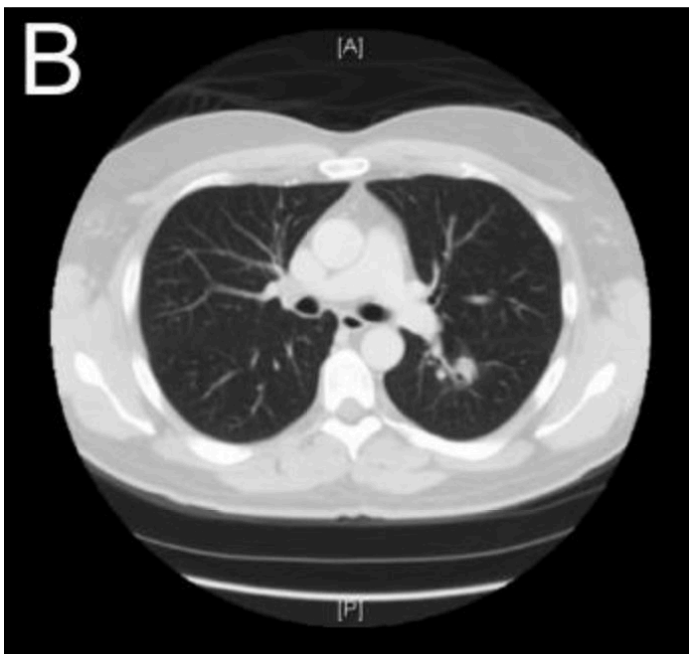


Figure 2. CT imaging of patient's pulmonary nodule. Reprinted from Byrnes EJ 3rd, et al. *PLoS One*. 2009,10;4(6):e5851. doi: 10.1371/journal.pone.0005851.

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Challenge Question 2. Which of the following would be the most likely histopathologic finding?

- A. Clotted blood from a previous hematoma
- B. Histology consistent with a rhabdomyosarcoma
- C. Tissue necrosis with thick-walled cavity containing narrow-based budding yeasts stained by Gomori methenamine silver stain
- D. Pus with many polymorphonuclear cells and gram-positive cocci
- E. Necrotic tissue with no tumor cells and no fungal elements observed but weakly acid-fast stained filamentous gram-positive organisms noted

Discussion

A. Clotted blood from a previous hematoma. For this diagnosis, the hematoma would need trauma and most likely would have resorbed or receded over 5 months.

B. Histology consistent with a rhabdomyosarcoma. The prebiopsy diagnosis was some type of neoplasm. However, a primary muscle tumor at 45 years of age would be unusual, and it does not explain the lung lesions unless these nodule(s) are metastatic disease.

C. Tissue necrosis with thick-walled cavity containing narrow-based budding yeasts stained by Gomori methenamine silver stain. The biopsy showed yeasts in the tissue. Mucicarmine and alcian blue stains were also performed, and both showed a prominently stained capsule around the yeasts. A Fontana-Masson stain of the tissue was also positive, demonstrating that this yeast produced substantial melanin. These histopath findings in the tissue helped to distinguish yeast from other fungi like blastomycosis.

D. Pus with many polymorphonuclear cells and gram-positive cocci. The mass could have been a staphylococcal abscess, but it continued to enlarge without evidence for inflammation or systemic symptoms. Furthermore, there was no involvement of the overlying skin.

E. Necrotic tissue with no tumor cells and no fungal elements observed but weakly acid- fast stained filamentous gram-positive organisms noted. With lung involvement and soft tissue involvement, the possibility of disseminated nocardiosis could be a possibility but is less likely in an apparently normal host.

Correct answer: C.

Culture Results

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In 3-4 days, the culture grew a mucoid yeast consistent with *Cryptococcus*. We now have confirmation that *Cryptococcus* was in the tissue, and probable disseminated disease with lung involvement, and no history of local trauma at the site for implantation of the fungus in tissue.

Challenge Question 3. What would you do next?

- A. Perform a serum cryptococcal antigen and start fluconazole at 400 mg/day
- B. Ask again for any CNS symptoms and if present, do a lumbar puncture (LP) to rule out CNS disease and if negative, one can treat without further work-up in an apparently normal host
- C. Check HIV test and CD4 count
- D. Surgically remove the large mass
- E. Perform a brain scan

Discussion

A. Perform a serum cryptococcal antigen and start fluconazole at 400 mg/day. A serum cryptococcal antigen is frequently performed to confirm if the *Cryptococcus* has disseminated from its original lung source. *Cryptococcus* can disseminate to any organ of the body. Although a skin or soft tissue cryptococcal infection is occasionally caused by direct inoculation of the yeasts into tissues, the vast majority of extremity or skin cryptococcosis cases represent disseminated disease. Many clinicians would start fluconazole at 400 mg to 800 mg/day as treatment for pulmonary infection in an immunocompetent patient. We will see later that the work-up may have needed to be more extensive. This case is likely disseminated disease with two non-contiguous sites of infection and not limited pulmonary disease.

B. Ask again for any CNS symptoms and if present, do a lumbar puncture (LP) to rule out CNS disease and if negative, one can treat without further work-up in an apparently normal host. *Cryptococcus* has a unique predisposition for dissemination to the central nervous system (CNS), and when *Cryptococcus* is found elsewhere in the body, the CNS should be considered a site for infection. In patients with CNS symptoms, a lumbar puncture should be performed to determine if *Cryptococcus* has entered the CNS. In patients with immunosuppressive conditions even without symptoms, a lumbar puncture should be performed to rule out CNS disease. However, over the last decade, there has been a movement away from the recommendations to perform lumbar puncture in asymptomatic, immunocompetent patients since the positive yield is so low¹.

C. Check HIV test and CD4 count. All patients with *Cryptococcus* isolated from any site should be screened with an HIV test and probably a CD4 count since idiopathic CD4 lymphocytopenia can present with disseminated cryptococcosis.

D. Surgically remove the large mass. Surgery is not mandatory with cryptococcosis cases, but a large granulomatous mass will not resolve quickly with antifungal treatment alone. Surgically removing the large mass will help more efficiently debulk the infection.

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E. Perform a brain scan. A brain scan is not initially performed in patients with normal neurological exams and no symptoms, such as this patient, but probably would have been helpful in hindsight after knowing what happened next.

Correct answer: In some respects, **A-E** all represent parts of reasonable next steps but rapid treatment with fluconazole (**A**) should be held until extent of disease is known.

Case Continued

The patient had a serum antigen titer (CrAg) of 1:32. As noted, his CT scan showed asymptomatic nodules in the lung. In fact, cryptococcosis of the lung often presents with single or multiple nodules, and biopsies for probable lung cancer will frequently yield *Cryptococcus*. However, pulmonary cryptococcosis can present in many forms from lung infiltrates to pleural effusions and can even produce acute respiratory distress syndrome or interstitial lung disease that looks like pneumocystis^{2,3}. Many of the myriad of pulmonary presentations depend on the immunocompetency of the host. The pulmonary site is likely the first organ to be infected with *Cryptococcus* if the host inhales either basidiospores or small poorly encapsulated yeasts. The yeast can cause acute pulmonary infection (pneumonia with symptoms) but more commonly goes into dormancy in a lymph node complex. The yeast is silent until the host's immune system deteriorates from an illness like HIV or from immunosuppressive drugs (eg, steroids, ibrutinb) and the yeast starts to grow again. When you detect a serum CrAg titer, the yeast likely has left the lung to disseminate. The CNS is a frequent location of dissemination, but many other organs can be sites of yeast dissemination as well.

This patient was HIV-negative with a CD4 count of 600 cells/mm³ and a serum CrAg of 1:32. He was started on fluconazole at 400 mg/day and did well, but 3 months later he had a seizure. At this time, he had a brain CT scan that showed a large, enhancing mass in the left parietal lobe and a similar appearing mass in the right cerebellar hemisphere.

Challenge Question 4. What should the next management step be?

- A. Perform lumbar puncture to determine if patient has meningoencephalitis
- B. Do a direct brain biopsy of an accessible brain lesion
- C. Check isolate for fluconazole susceptibility and determine whether the yeast is *C neoformans* or *C gattii*
- D. Add corticosteroids to the treatment regimen
- E. Stop fluconazole treatment and start liposomal amphotericin B plus flucytosine combination therapy

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Discussion

A. Perform lumbar puncture to determine if patient has meningoencephalitis. The lumbar puncture might help define meningitis, and since the patient was on fluconazole, it may or may not be culture positive. Also, with these multiple parenchymal lesions, there may be some concern about increased intracranial pressure and a lumbar puncture could lead to herniation. So, the neurosurgery team should be involved before an LP.

B. Do a direct brain biopsy of an accessible brain lesion. A brain biopsy would be direct and likely definitive for mass identification. Although this patient appears to be a normal host, this strategy can help rule out cancer or other infections like nocardia, tuberculosis, or other causes of microbial brain abscesses. The patient could have more than one infection. The negative aspect of this strategy is that a brain biopsy could have a small complicating risk to the patient.

C. Check isolate for fluconazole susceptibility and determine whether the yeast is *C neoformans* or *C gattii*. Since it seems like the patient has possible persistence of infection, it may be reasonable to check the fluconazole in vitro susceptibility of the isolate. Actually, there are very few primary azole-resistant cryptococcal strains. Admittedly, there are criteria for in vitro susceptibility testing, but there are no clear breakpoints yet for cryptococcosis⁴. Most consider MICs below 16 mcg/mL as a susceptible strain to fluconazole and MICs greater than 16 mcg/mL as resistant. At an MIC of 16mcg/mL for fluconazole, it can be difficult to discern if there is therapeutic resistance or not, but elevated fluconazole doses are commonly used at this MIC level⁵. As was done in the beginning of treatment, the isolate was saved, and an MIC was not initially performed. An interesting issue is whether to determine the cryptococcal species. This becomes relevant in two aspects: (1) he had travelled to an area in which *C gattii* is endemic in the environment and (2) cryptococcomas in the brain have been observed more frequently in *C gattii* than *C neoformans* CNS infections⁶. Thus, epidemiologically, it would be interesting to know the specific species. That said, despite some slight difference in MICs and clinical presentation, all studies to date have not shown that speciation would inform a different treatment strategy^{7,8}. At present, cryptococcal meningoencephalitis is treated similarly for both *C neoformans* and *C gattii*. However, some experts might extend the induction period with *C gattii* meningitis in normal hosts.

D. Add corticosteroids to the treatment regimen. The addition of corticosteroids to treat brain edema has not been found to be beneficial, and in fact, corticosteroids can reduce the fungicidal activity of the direct antifungal treatments. Therefore, it is important to understand how well the fungal burden is being controlled throughout treatment. On the other hand, an overabundance of inflammation caused by an Immune Reconstitution Inflammatory Syndrome (IRIS) may need to be controlled by corticosteroids but only after fungal burden is assessed.

E. Stop fluconazole treatment and start liposomal amphotericin B plus flucytosine combination therapy. It is now likely that the patient has CNS involvement and, in this situation, liposomal amphotericin B and flucytosine induction therapy will be necessary rather than fluconazole monotherapy. Since this will require

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long-term antifungals, the clinician may be encouraged to properly stage/document the CNS infection before starting an empirical regimen.

Correct answer: A-E all have some truth to them and might be successful avenues of care for the patient.

Biopsy and MIC Results

In this particular patient, the clinician followed strategy **B** first and performed a brain biopsy. It showed granulomatous inflammation with budding yeasts and grew *Cryptococcus*. Now, we can answer 3 things. First, we clearly had dissemination of *Cryptococcus* to the CNS. The patient's infection was all one pathogen with no co-infection. Second, we had both the original yeast isolate and the CNS yeast isolate. Microbroth dilution MICs were performed and both isolates had MICs of 8 mcg/mL to fluconazole. Importantly, we did not see a rise in MICs with the second isolate. The MIC was somewhat high, but the isolate should respond to standard fluconazole treatment and should not be considered directly resistant.

Third, it was possible for us to check the cryptococcal species. This isolate was indeed *C gattii* with a genotype of VG1. It is likely that he acquired this strain while he was visiting the San Francisco area. The classic Northwestern USA outbreak strains are VGII^{a/b/c} but VG1 is also found in California⁹. However, we are now starting to see more *C gattii* infections in patients east of the Mississippi with no travel history, possibly in relation to climate change. Furthermore, the clinician may assume that this was a relapsed case associated with fluconazole monotherapy, since it can be notoriously poor for CNS cryptococcosis treatment. In this case, 3 months of azole treatment had not sterilized the brain tissue. Therefore, focus with a polyene-containing combination regimen was necessary. The patient was started on liposomal amphotericin B 4 mg/kg/d and flucytosine 100 mg/kg/d.

So far, this case has demonstrated 2 features to consider. First, in the original work-up, there was evidence of disseminated disease (lung and muscle) and disseminated disease should be induced similarly to CNS disease. Second, with evidence of disseminated disease, a more aggressive CNS work-up may be of value.

Challenge Question 5. After a week of combination therapy, his creatinine had risen to 2.5 mg/dL and a therapeutic change was considered. What would you do now?

- A. Stop combination therapy and switch back to fluconazole monotherapy at 800-1200 mg/d
- B. Reduce the liposomal amphotericin B dose to 3 mg/kg/d and continue flucytosine with aggressive saline infusion before and after drug infusions
- C. Stop antifungals for 3-5 days to rest the combination of liposomal amphotericin B and flucytosine and allow kidneys to improve
- D. Switch to fluconazole 1200 mg/d plus reduced doses of flucytosine
- E. Attempt triple-drug therapy with reduced doses of polyene in the regimen

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Discussion

A. Stop combination therapy and switch back to fluconazole monotherapy at 800-1200 mg/d. The use of fluconazole monotherapy during the induction period is never a good idea, especially if the host has a high burden of yeasts. There are elegant studies showing the plasticity of the cryptococcal genome under stress. Within the host, both tolerance and heteroresistance mechanisms occur, and these changes make monotherapy fail¹⁰. A few studies¹¹ suggest that fluconazole monotherapy can work in normal hosts for refractory disease, but considering the brain involvement in this patient, fluconazole monotherapy for induction therapy is probably not a good idea.

B. Reduce the liposomal amphotericin B dose to 3 mg/kg/d and continue flucytosine with aggressive saline infusion before and after drug infusions. Reduced risk for renal dysfunction (as compared with conventional amphotericin B), which leads to a lower propensity for induction therapy interruption, is the reason why liposomal amphotericin B has become the polyene of choice in cryptococcal meningoencephalitis. However, even this formulation can have nephrotoxicity issues. Balancing the dose for efficacy and safety can lead to challenging bedside decisions, but from a therapeutic standpoint, you can safely drop the dose of liposomal amphotericin B to 3 mg/kg/d¹². In addition, with careful attention to the kidney function, saline loading around the dose may help reduce nephrotoxicity. Thus, this strategy may enable the clinician to get at least 2 weeks of induction therapy into the patient.

C. Stop antifungals for 3-5 days to rest the combination of liposomal amphotericin B and flucytosine and allow kidneys to improve. Some clinicians will stop the polyene for several days hoping that the kidneys will recover. The half-life of the polyene is long and there are recent strategies of trying intermittent polyene therapy. However, at this point, aggressive and consistent combination therapy is desired during the induction period. This is especially true of those with a high burden of yeasts in the CNS and possibly of those with high amounts of invading yeasts, as marked by such large cryptococcomas in the tissue. Thus, stopping and starting therapy is not encouraged.

It has been noted that a risk factor for failure is drug interruption of the 2-week induction phase. The question will also be whether you can get the recommended 4-6 weeks of combination induction therapy for the patient¹³. This will be a bedside decision. One could consider that he had 1 week of combination therapy with polyene and flucytosine and this was successful in the ACTA study¹⁴, but it is not clear whether similar results would occur in resource-available health care systems. Furthermore, this particular patient has multiple cryptococcomas, so most experts encourage a longer induction period with combination therapy.

D. Switch to fluconazole 1200 mg/d plus reduced doses of flucytosine. If one cannot feel comfortable in tolerating further polyene toxicity, the fluconazole and flucytosine combination may work here^{15,16}. As noted, the doses in this scenario are high for the patient's present renal function. First, you could probably reduce the fluconazole dose to 800 mg/d until renal function returns to normal. Second, the flucytosine must be adjusted. There are nomograms for flucytosine dosage during renal dysfunction¹⁷, but a simple calculation is to reduce the dose by half as renal function drops to half-normal and by a quarter as renal function is one quarter of

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normal. The recommended dosage continues to drop further with severe renal dysfunction or dialysis dependency. It is also recommended that flucytosine levels be checked at 2 hours post dose after 3-5 doses and then periodically with changes in renal dysfunction. It is recommended that the flucytosine level be kept between 30-80 mcg/mL since toxicity starts to occur at 100 mcg/mL and above. Many clinicians do not have access to rapid flucytosine levels and thus will have to carefully follow frequent complete blood counts to watch for development of cytopenias. There has been a moderate amount of data suggesting that the fluconazole and flucytosine combination is not an inferior induction regimen, although at present, the polyene combination with flucytosine is the preferred induction regimen.

E. Attempt triple-drug therapy with reduced doses of polyene in the regimen. Reducing the dose of polyene and then adding an azole along with flucytosine is an interesting strategy. The use of triple-drug therapy for cryptococcal meningoencephalitis has both positive and negative data. Therefore, it becomes a bedside decision based within the context of the individual case. Triple-drug therapy is a possibility but generally is only used in unique or very difficult-to-treat cases and is not a routine regimen for induction therapy. However, recent data with the AMBITION Study in HIV-infected patients showed triple-drug therapy as an effective regimen, which could be adapted to this patient¹⁸.

Correct answer: B.

Summary of Special Issues Regarding C neoformans and C gattii

This patient has multiple unique features that illustrate several important principles. First, this patient is apparently immunocompetent, which only occurs in 10-20% of non-HIV-infected cryptococcosis patients¹. Although it is possible that there may be some underlying disease in immunocompetent patients, it is difficult to find the immune defect without additional testing. However, it is always reasonable to check an HIV test, CD4 count, and anti-granulocyte macrophage colony stimulating factor (GM-CSF) antibody in the apparently normal host. Both idiopathic CD4 lymphocytopenia¹⁹ and anti-GM-CSF antibody syndrome²⁰ have been described as underlying immune causes in apparently normal hosts. The anti-GM-CSF antibody syndrome is particularly seen in patients with *C gattii* infection.

Second, this *C gattii* case is somewhat unusual since it does initially appear to follow an endemic focus. For instance, *C gattii* is typically associated with tropical and subtropical climates, including Australia and South America. However, there have been outbreaks in temperate climates, including Vancouver Island, mainland British Columbia, Canada, and the USA Pacific Northwest, including Washington and Oregon. There have also been cases in Europe and Africa. Therefore, *C gattii* already has a wide distribution and seems to be spreading, possibly because of global warming. The yeasts (both *C neoformans* and *C gattii*) are typically associated uniquely with trees such as mopane and eucalyptus (*C gattii*), and *C neoformans* is also frequently associated with pigeon guano. Occasionally a case can be linked to an environment exposure, but most cases cannot, and the reactivation pathophysiology makes it even more difficult to determine infection source. In this case, however, it is likely that the patient was initially infected on the West Coast of the USA five months prior to symptom development.

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Third, the literature frequently suggests that *C gattii* infects immunocompetent patients, and while true in this case, *C neoformans* can also infect normal hosts⁶. Furthermore, *C gattii* more easily infects immunocompetent individuals likely because of more intense exposure time rather than because of unique pathophysiology. As previously mentioned, *C neoformans* and *C gattii* are treated similarly, and outcomes are also similar with the same underlying disease. In fact, length of symptomatic infection may be more controlling of patient outcome than the species of yeast.

Fourth, this case emphasizes one major difference between *C gattii* and *C neoformans* infections. Although both can cause cryptococcomas, *C gattii* produces them much more frequently than *C neoformans* as a percentage of their total CNS infections. With cryptococcomas, there are three clinical issues: (1) The value of surgical debulking of lesions is not precise. It is suggested that lesions greater than 3-5 cm may need surgical attention and possible removal. Surgery will need to be a bedside decision; (2) It is recommended that induction therapy period be prolonged such as 6 weeks and consolidation/suppression be continued for at least 2 years. These recommendations are based on expert opinion rather than precise clinical trials. However, radiographically these lesions may enlarge with IRIS and persist for long periods of time without serious consequences²¹; (3) It is less of a concern for apparently normal hosts, but for the immunocompromised host, these brain parenchymal lesions might represent another pathogen such as nocardia or tuberculomas. In our case, brain biopsy confirmed cryptococcal involvement, but the use of biopsy becomes a clinical decision at the bedside.

Case Continued

This patient received liposomal amphotericin B 4mg/kg/d and flucytosine for 3-4 weeks, but the nephrotoxicity became difficult to manage. Eventually, the patient was placed on fluconazole 800 mg/d because of reduced renal function, and he did not receive a complete 6-week combination induction regimen.

The patient is now at 6 weeks of treatment for CNS cryptococcosis. He has some weakness, dizziness, and mild headache. His neurological examine is normal.

Challenge Question 6. What would you do?

- A. Continue fluconazole and recheck CT scan
- B. Renal function has improved and thus restart liposomal amphotericin B and fluconazole
- C. Obtain MRI scan and perform LP
- D. Do nothing but check a serum CrAg and just observe if there is no change
- E. Call a neurosurgeon

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Discussion

As one thinks about post induction therapy complications in this patient, the following triad of issues are considered: (1) development of drug resistance; (2) development of hydrocephalus; (3) development of IRIS. If the patient was receiving the combination induction therapy followed by high-dose azole consolidation therapy, it would be unlikely for yeast drug resistance to develop. However, the other two complications of hydrocephalus and IRIS are definitely a possible complication at this time in the course of infection.

A. Continue fluconazole and recheck CT scan. This is not the preferred option, as access to the CNS would be desirable.

B. Renal function has improved and thus restart liposomal amphotericin B and fluconazole. This is not the preferred option, as access to the CNS would be desirable.

C. Obtain MRI scan and perform LP. The most reasonable response to this clinical development is to access the CNS rather than change any treatment regimen. This will be done most precisely with both an MRI scan for evidence of hydrocephalus and a careful assessment of leptomeningeal inflammation, edema, or enlargement of the cryptococcomas. After an MRI scan and, if safe to do, lumbar puncture would be considered to access the CNS. Evidence of inflammation from CSF analysis (a negative CSF culture and/or PCR and/or reduced CrAg titer) or MRI scan would suggest that symptoms might be related to IRIS and that corticosteroids may need to be considered depending on severity of signs and symptoms. It is important to emphasize that cryptococcal IRIS can occur in HIV patients, transplant recipients, and normal hosts²²⁻²⁴. Of course, hydrocephalus may need to be managed by a shunt and it is generally safe to put shunts in once a patient has started effective antifungal agents²⁵.

D. Do nothing but check a serum CrAg and just observe if there is no change. It is important to emphasize that generally serum CrAg tests are not helpful in following treatment of disseminated cryptococcosis. However, sometimes CSF CrAg reductions during treatment and a negative PCR will aid in favoring IRIS over relapsed infection.

E. Call a neurosurgeon. This is not currently required as the CNS can be accessed via an LP unless there is concern about herniation.

Correct answer: C.

MRI and LP Results

The patient had an MRI scan that showed no enlargement in the cryptococcomas, no hydrocephalus, and mild leptomeningeal inflammation. The LP was culture and PCR negative with normal glucose and protein and 20 nucleated cells/mm³. The patient was treated with nonsteroidal anti-inflammatory drugs (NSAIDS) and his headache and other symptoms resolved. It was felt that he did not need neurosurgical intervention, and

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corticosteroids were not necessary because symptoms were mild. He was continued on fluconazole adjusted for his renal improvement.

Challenge Question 7. The long-term management of cryptococcal meningoencephalitis continues to be poorly studied and has been recently directed by studies from the HIV literature. What is the next management step?

- A. Continue fluconazole for 2 years with little need for follow up
- B. Stop fluconazole suppression at 3 months since patient is a normal host
- C. Follow MRI scan and stop fluconazole when lesions have reduced by 50%
- D. Continue fluconazole for 2 years and continue frequent follow up since there may be substantial morbidity issues that need to be addressed
- E. Because of brain parenchyma involvement the patient will need lifelong therapy, especially if serum CrAg remains positive

A. Continue fluconazole for 2 years with little need for follow up. Two years of fluconazole for brain cryptococcomas is recommended for follow up by 2010 Infectious Diseases Society of America (IDSA) Guidelines¹¹. However, this is not the best step since the patient will need to be followed up closely.

B. Stop fluconazole suppression at 3 months since patient is a normal host. This should not be carried out as the treatment duration is too short—2 years is recommended by the 2010 IDSA Guidelines¹¹.

C. Follow MRI scan and stop fluconazole when lesions have reduced by 50%. Frequently, it takes time for the scans to return to normal, and imaging correlation with outcome is still not well integrated.

D. Continue fluconazole for 2 years and continue frequent follow up since there may be substantial morbidity issues that need to be addressed. This is the best strategy as 2 years of fluconazole for brain cryptococcomas is recommended for follow up by 2010 IDSA Guidelines¹¹. Most recommendations support following and treating HIV patients for a year with fluconazole for meningoencephalitis alone. While there is no precise data regarding non-HIV infected patients, most patients with CNS disease who relapse will do so in that first year. Two years of fluconazole is a guess for optimal length of therapy because of the deep-seated location of the CNS cryptococcomas, but it could be shorter. Frequently, it takes time for the scans to return to normal and imaging correlation with outcome is still not well integrated. Also, these patients need close follow up. A recent longitudinal cohort for HIV-negative patients showed that very low initial Montreal Cognitive Assessment (MOCA) scores were associated with poor long-term cognition issues²⁶.

In patients with non-HIV CNS disease, there were frequent complications requiring repeat lumbar punctures and ventriculostomies. In older patients (≥ 60 years of age), there was an association with death in the 2-year follow-up period. Despite aggressive therapy, CNS cryptococcosis is characterized by substantial long-term neurologic sequelae^{26,27}. However, we have no data that patients need lifelong therapy, even when CrAg remains positive for years. The patient should be followed closely, and initial therapy with fluconazole is considered for 1 year with meningitis and 2 years with cryptococcoma(s).

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E. Because of brain parenchyma involvement the patient will need lifelong therapy, especially if serum CrAg remains positive. Although patients with cryptococcomas may need 2 years of therapy, lifelong therapy is not recommended.

Correct answer: D.

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