CASE 3: 45-YEAR-OLD GAY MAN WITH A NON-HEALING ULCER

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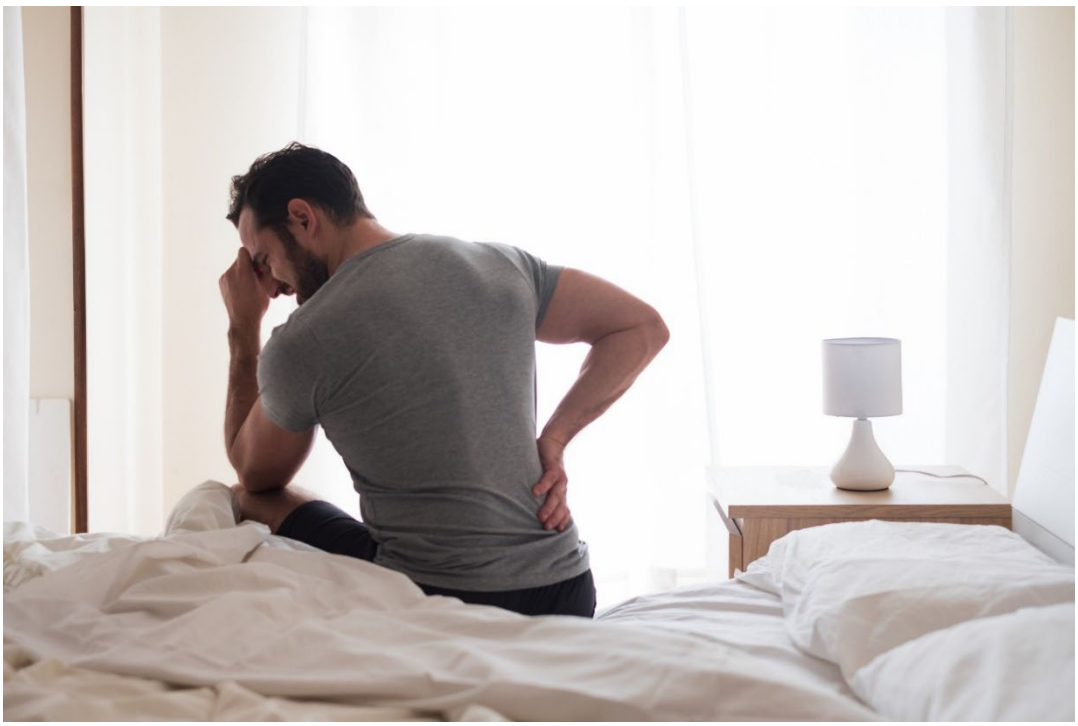

Initial Presentation

A 35-year-old white gay man presented to the emergency room in the Southeastern United States with a non-healing ulcer on his forehead. In a general review of symptoms, he described a mild persistent headache for several weeks. He denied fever or weight loss. He has had multiple sexual partners with whom he has had unprotected sex. He has not been tested for human immunodeficiency virus (HIV), has not sought medical care recently, and has been on no medications. His physical examination was normal except for the skin lesion on his forehead (See Figure 1) which had appeared and grown over the last month.

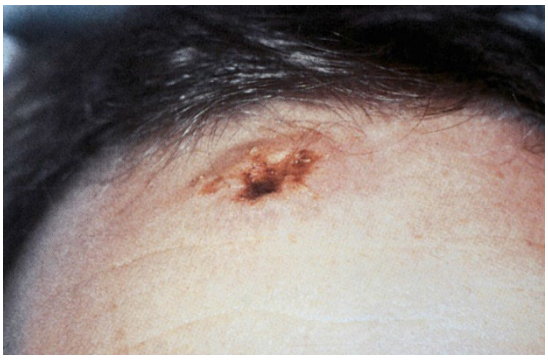

Figure 1. Non-healing ulcer on the patient's forehead. Image courtesy of John R. Perfect.

Challenge Question 1. What would be the next step in your evaluation?

A. Send the patient to a dermatologist for evaluation
B. Since he doesn't have history of fevers and his present temperature is normal, it is highly unlikely that infection is causing his signs and symptoms
C. Test for HIV and send patient to Infectious Disease Clinic
D. With this patient's risk factors and nonhealing skin lesion, do a biopsy in the ER for culture
E. With the risk factors and the history of persistent headaches, the skin lesion may reflect a more disseminated infection, so do a rapid HIV test in the ER and if positive, a lumbar puncture (LP) would be indicated in the ER

Discussion

A. Send the patient to a dermatologist for evaluation. This will likely delay diagnosis; other tests can be performed initially to move your evaluation forward more quickly.

B. Since he doesn't have history of fevers and his present temperature is normal, it is highly unlikely that infection is causing his sign and symptoms. This cannot be assumed, and with the patient's risk factor history and because of his geographic location, several potential infections may be causing the lesion and must be directly investigated.

C. Test for HIV and send patient to Infectious Disease Clinic. A rapid test for HIV could be done in the ER which would speed up the evaluation, but there are more steps to take.

D. With this patient's risk factor and a nonhealing skin lesion, do a biopsy in the ER for culture. Culture would likely take some time to report, and with the patient's risk factors, other more rapid tests would be preferable.

E. With the risk factors and the history of persistent headaches, the skin lesion may reflect a more disseminated infection, so do a rapid HIV test in the ER and if positive, a lumbar puncture (LP) would be indicated in the ER. This would be the preferred option with a rapid HIV test to confirm the risk-factor analysis, as the patient is likely infected with HIV. This rapid test was found to be positive and with some central nervous system (CNS) symptoms, the immediate diagnostic focus would be a lumbar puncture to rule out cryptococcal meningitis in this locale. Of course, he could have tuberculous or *Histoplasma* meningitis or even a CNS brain lesion with infection or tumor. However, it is important that the clinician has context about the patient's geographical location. The patient lives in the South-eastern United States, and it is therefore unlikely that this symptom complex is either tuberculosis or histoplasmosis. He also has no travel history, thus coccidioidal disease is unlikely. In Southeast Asia, HIV-infected patients typically present with skin lesions (80%) and disseminated *Talaromyces* infection[1], but there is simply no exposure in this case. Even with a normal neurological exam and no papilledema, many clinicians would send the patient for a computed tomography (CT) scan to look for space-occupying lesions prior to lumbar puncture, but this is probably an

over cautious approach. However, if the CT scan is done, it should not provide a substantial delay in care during the ER visit for patients who are not severely ill. Also, with the lateral flow assay (LFA), a rapid serum CrAg test can be performed before lumbar puncture to enhance the potential for diagnosis of cryptococcal meningitis[2].

Correct answer: E.

Test Results including CT and LP Results

The patient is tested for HIV, and the results are positive. The CT scan was normal except for a slight decrease in brain parenchymal size for stated age, which might reflect the chronicity of his HIV infection.

The lumbar puncture was performed with the following results: opening pressure (OP) was 300 mm of CSF. CSF nucleated cells were 5/mm^3; India ink-positive; glucose 30 mg/dL; protein 85 mg/dL, and cryptococcal antigen titer (CrAg) was >1:640; CSF was sent for culture.

Challenge Question 2. With these results, what is important?

A. Opening pressure is important and should be measured in all patients, and results should be taken into consideration for future management issues
B. The CSF results describe meningitis with a relative leukopenia, and this has some prognostic features associated with it
C. The CSF glucose is low (hypoglycorrhachia) and could provide prognostic and diagnostic features since there are a variety of causes for hypoglycorrhachia (bacterial meningitis, fungal meningitis, rarely viral meningitis, mycobacterial meningitis, carcinomatosis, sarcoidosis, and drug reactions)
D. The India ink is positive, and appearance of the encapsulated yeasts confirms the diagnosis of cryptococcal meningitis
E. The CrAg is high and suggests a high burden of yeasts in the CNS

Discussion

A. Opening pressure is important and should be measured in all patients, and results should be taken into consideration for future management issues. Increased intracranial pressure and its management is extremely important to the outcome of HIV-infected patients with high-burden yeast infections[3]. Although the pathophysiology for this increased open pressure is not always certain, many believe the yeasts physically plug up the CSF resorption capacity of the arachnoid villi, producing an outflow obstruction thus elevating the pressure in the dynamic but enclosed compartment. It is possible that the diffuse extracellular polysaccharide antigen could add to the cerebral edema, however, mannitol and acetazolamide treatments do not improve symptoms or outcome. They are not recommended for treatment of increased intracranial pressure in this type of patient. The routine uses of corticosteroids as recommended in tuberculous meningitis is not helpful here. In fact, early use of dexamethasone (DEXA) in a randomized blinded study showed that the DEXA group

had higher morbidity, more adverse events, and reduced antifungal activity with no positive impact on outcome[4]. Thus, corticosteroids are not recommended in early management of cryptococcal meningitis unless it is considered a component of immune reconstitution inflammatory syndrome (IRIS) causing disease. Therefore, the focus on controlling OP has been through local CSF drainage. Daily LPs have been suggested to reduce OP to under 200 mm or by half for high CSF pressures[5]. Although the preciseness of lowering OP is not well studied, the value of repeated follow-up LP's have been described[6]. Generally, LPs are performed daily until pressure is reduced to a stable level and CNS symptoms are eliminated. If LPs are required for more than a few days, then consideration of a lumbar drain or ventriculoperitoneal (VP) shunt is worthwhile. Increased intracranial pressure and its control has major prognostic features; removal of CSF can relieve symptoms and eventually reduce the high CSF pressures. It is less clear how asymptomatic elevated OPs should be managed for final outcome, but most clinicians err on the side of trying to acutely reduce increased OPs.

B. The CSF results describe meningitis with a relative leukopenia, and this has some prognostic features associated with it. For a cryptococcal meningitis or any infectious meningitis, 5 nucleated cells/mm^3 in CSF demonstrate a paucity of immune cells and, in this case, reflects the profound cellular immune depression of the patient. CSF leukopenia in cryptococcal meningitis is a risk factor for both treatment failure and the development of IRIS[7]. Along with CSF host cell numbers, there have been some investigations into the CSF inflammatory mediators and their prognostic insights. One of the most critical mediators is gamma interferon, which tends to be low in patients with poor prognoses[8]. This finding along with two positive studies that utilized recombinant gamma interferon in the management of cryptococcal meningitis make this immune enhancement a potential therapeutic option[9,10]. However, it generally continues to be ranked as second line or alternative therapy for refractory diseases. Reasons for the reduced use of this apparently effective therapy are not clear but are likely due to costs and concerns about producing an IRIS picture with too much immune stimulation. However, early studies have not found this to be the case.

C. The CSF glucose is low (hypoglycorrhachia), which could provide some prognostic and diagnostic features since there are a variety of causes for hypoglycorrhachia (bacterial meningitis, fungal meningitis, rarely viral meningitis, mycobacterial meningitis, carcinomatosis, sarcoidosis, and drug reactions). Low CSF glucose has both diagnostic and prognostic features. We do not have a serum glucose, but at this patient's level, it is likely to be less than the normal two-thirds standard of a simultaneous serum level. In cryptococcal meningoencephalitis, a low CSF glucose has been considered a poor prognosis for successful management both before and during the HIV pandemic. It is encouraging when the CSF glucose returns rapidly to normal. In some geographical areas with high TB endemicity, co-infection with *Cryptococcus* and *Mycobacterium* tuberculosis may occur and further contribute to the low CSF glucose.

D. The India ink is positive, and appearance of the encapsulated yeasts confirms the diagnosis of cryptococcal meningitis. The India ink test has been discontinued in many laboratories throughout the world for multiple reasons. Firstly, it was user dependent. Secondly, there was less quality control over its evaluation. Finally, the lateral flow assay (LFA) for CrAg detection is so fast and cheap that it can easily substitute for the India ink. However, in experienced hands, India ink microscopy is positive in 80% of patients with cryptococcal meningitis and HIV and in 50% of samples in all other risk groups. During infection, the India

ink test will frequently be positive in follow-up LPs even when cultures are negative. These yeasts are considered dead yeasts and do not alter the management plan. Finally, it takes 10^3 CFU/mL CSF of yeasts to obtain a positive India ink screen. With the use of quantitative CSF yeast cultures, it has been shown that HIV-infected individuals with initial presentation may frequently have 10^6-10^7 CFU of yeasts/mL CSF on presentation[11].

E. The CrAg is high and suggests a high burden of yeasts in the CNS. In this patient the CrAg was high, which suggested a large burden of yeasts in the CSF (eg, ~10^6 CSF/ml). This high CrAg has implications for outcome. High titer CrAg positive patients are at risk for failure, so the titer may be helpful in an approach to treatment and follow-up along with more frequent LPs to ensure a fungicidal response. The CrAg is the "best serological test" in mycology. It has a very high sensitivity and specificity, and the prior latex agglutination/ELISA tests have compared favorably with the lateral flow assay (LFA). The LFA test is dipstick technology and is rapid, cheap, and can provide some semi-quantitative analysis (titers)[12]. Titers for LFA tend to be approximately 4 times higher than latex agglutination titers, which is important to understand. As good as the diagnostic test is for CrAg, it is less precise in its use to follow the patient during treatment[12]. The serum CrAg does not mirror response to treatment and may continue to be positive for years after successful treatment. The titer for the CSF CrAg may start to decrease with effective therapy, but its drop is not precise. However, when deciding on the diagnosis of IRIS, a reducing CrAg CSF titer is encouraging.

Correct answer: Options **A-E** all add important features to this case and its management.

Summary of CrAg Screening

In an attempt to use the serum CrAg to identify cryptococcal meningoencephalitis in high-risk patients earlier in the course of their disease, there is now a focus on CrAg screening in newly diagnosed HIV-infected patients. CrAg screening is particularly focused on those with CD4 counts below 100 cells/mL and in regions of the world where serum CrAg positive prevalence is 2% or greater[13-15]. This improves the cost-benefit analysis. Many parts of sub-Saharan Africa have this prevalence of disease, and even in a USA cohort[16], prevalence reached approximately 3%. Therefore, point-of-care screening will pick up positive CrAgs, and some of these patients will have symptoms but others will be asymptomatic. In resource-available health care systems, a positive CrAg in an HIV patient requires an LP to rule out CNS disease. If negative, a patient will be placed on pre-emptive treatment with fluconazole at 400 mg/d. In resource-limited areas where LPs may be more difficult to perform, clinicians will rely on symptoms and CrAg titers (≥1:160) to decide whether to do an LP. If patients are asymptomatic and the CrAg is low, they may start pre-emptive fluconazole without an LP. With this strategy, recent studies clearly show that a positive CrAg at the beginning of therapy identifies a poorer outcome. In addition, a high CrAg titer (≥1:160) represents a patient with a high burden of yeasts, and even with a negative LP, the risk for eventual CNS disease is high and failure of pre-emptive fluconazole (even 1200 mg/d) is substantial[13-15,17]. Thus, studies are now beginning to treat asymptomatic, high-titer CrAg patients with either single-dose liposomal amphotericin B with oral fluconazole or with the combination of fluconazole and flucytosine. Although CrAg screening utilization and the optimal management of asymptomatic CrAg require further studies, the early identification of infection with proficient testing systems has a major impact

on the successful management of patients with cryptococcal infection and should be carefully implemented in health care systems where disease occurs.

Challenge Question 3. The lumbar puncture results and brain scan are available, and culture is pending for this patient. What is/are the next step/s?

A. Patient should have a CD4 count test and HIV load sent and should be admitted to a hospital with pain meds awaiting culture results
B. Patient should have a full blood count taken, and if normal, the patient should be admitted and given fluconazole (1200 mg/d) monotherapy
C. Patient should be started on liposomal amphotericin B 3-4 mg/kg/d IV and flucytosine 100 mg/kg/d orally on hospital admission
D. Patient is stable and should be sent home on an all-oral regimen of fluconazole 1200 mg/d plus flucytosine 100 mg/kg/d to be followed in the clinic
E. Patient should be admitted and started on liposomal amphotericin B plus fluconazole 800 mg/d.
F. Give a single dose of liposomal amphotericin B at 10 mg/kg x 1 plus oral flucytosine (100mg/kg/d) and fluconazole (1200mg/d) for 14 days

Discussion

A. Patient should have a CD4 count test sent and should be admitted to a hospital with pain meds awaiting culture results. There is no point in waiting since a patient with HIV infection and a positive India ink or CSF CrAg detection has cryptococcal meningoencephalitis at a minimum and should be started on therapy.

B. Patient should have a full blood count taken, and if normal, the patient should be admitted and given fluconazole (1200 mg/d) monotherapy. Fluconazole monotherapy should not be used for induction therapy in cryptococcal meningitis[18]. The failure rate is too high and reflects the in vivo resistance of the dynamic yeast under stress involving heteroresistance or tolerance mechanisms[19]. These mechanisms can be observed in human infections, but this phenomenon is not a stable phenotype and is frequently not captured by standard in vitro susceptibility in which most cryptococcal isolates are reported as susceptible.

C. Patient should be started on liposomal amphotericin B at 3-4 mg/kg/d IV and flucytosine 100 mg/kg/d orally on hospital admission. This is the preferred regimen in resource-available health care systems since the combination of polyene and flucytosine is the most fungicidal combination and has even shown a survival benefit. Liposomal amphotericin B is generally favored above amphotericin B deoxycholate because of reduced toxicity and decreased chance of interrupting therapy[20].

D. Patient is stable and should be sent home on an all-oral regimen of fluconazole 1200 mg/d plus flucytosine 100 mg/kg/d to be followed in the clinic. Fluconazole plus flucytosine as an all-oral regimen had a satisfactory outcome in recent studies[21-24] but is somewhat discouraged because hospital care in the first 1-2

weeks may be important to early management of complications.

E. Patient should be admitted and started on liposomal amphotericin B plus fluconazole 800 mg/d. Studies show that the regimen of polyene plus fluconazole[25] has a reasonable but less desirable outcome when flucytosine is not available. If this regimen is chosen, it is encouraged that at least 800 mg/d of fluconazole is used.

F. Give a single dose of liposomal amphotericin B at 10 mg/kg x 1 plus oral flucytosine (100mg/kg/d) and fluconazole (100mg/kg/d) for 14 days. For resource-limited health care systems, the large phase 3 AMBITION study[26], which utilizes animal studies and a validating phase 2 study, examined the long half-life of liposomal amphotericin B in tissue. As recently reported, the phase 3 trial examined the use of a single dose of liposomal amphotericin B 10 mg/kg combined with 14 days of flucytosine 100 mg/kg/d and fluconazole (1200 mg/d) vs the 7-day AmB course (with 7 days of flucytosine 100mg/kg/d then 7 days of fluconazole 1200mg/d) that is standard of care. This study, conducted in HIV-infected patients in Africa with cryptococcal meningitis, demonstrated the non-inferiority and potential kidney-sparing effect of the simpler regimen in a resource-limited setting and has become the WHO primary recommendation for cryptococcal meningitis in those with HIV infection. Whether this regimen becomes standard in resource-available health care system will require further experience.

Correct answer: C or F.

Case Treatment

The patient was started on liposomal amphotericin B 4 mg/kg/d[27] and flucytosine at 100 mg/kg/d. Because of high OP and persistent headaches, the patient also had daily LPs until his headaches resolved and OP pressure stabilized.

Challenge Question 4. What is the next management step?

A. Since HIV immunosuppression is a major cause of cryptococcal disease in this patient, antiretroviral therapy (ART) therapy should be started with the beginning of antifungal therapy
B. Like for tuberculous meningitis, a dexamethasone taper should be started with antifungal therapy for this CNS infection
C. Induction therapy with liposomal amphotericin B and flucytosine should be continued for 6 weeks
D. Liposomal amphotericin B and flucytosine should be continued for 2 weeks of induction therapy and then switched to consolidation phase with fluconazole 800mg/d
E. Serum and CSF CrAg titers should be followed closely for first 10 weeks of therapy

Discussion

A. Since HIV immunosuppression is a major cause of cryptococcal disease in this patient, antiretroviral therapy (ART) therapy should be started with the beginning of antifungal therapy. Both a comparative COAT study and a reviewing meta-analysis make it clear that the start of ART during the first 2 weeks of antifungal therapy leads to worse outcomes compared to delayed ART[28]. It is not certain what causes these deaths, but the correlation between starting ART early and early death appears to be real. There was consideration that early ART creates complicating IRIS, and while it could be true, it has been difficult to prove. The general recommendation is to start ART between 4-6 weeks after starting antifungal therapy. The start time could be delayed longer in resource-available health care systems up to 10 weeks with the conclusion of consolidation therapy but commonly is given at 4-6 weeks after start of therapy.

B. Like tuberculous meningitis, a dexamethasone taper should be started with antifungal therapy for this CNS infection. The DEXA study from Asia showed that corticosteroids during early induction therapy had no benefit and actually caused increased morbidity and reduced antifungicidal activity[4]. Thus, early corticosteroids should not be used unless the clinician feels the patient has entered an IRIS phase which may require treatment with anti-inflammatories such as corticosteroids[29,30].

C. Induction therapy with liposomal amphotericin B and flucytosine should be continued for 6 weeks. The early studies of staged therapy (induction, consolidation, and suppression) for cryptococcal meningitis in HIV-infected patients used a 2-week course for the endpoint of induction therapy, since at this time most patients had sterile CSF and resolved symptoms/signs. Recently, an ACTA study[21] in a resource-limited setting suggested that 1 week of amphotericin B plus flucytosine had a better outcome then 2 weeks of combination therapy. The concern for using this study in resource-available health care systems is that it is not clear whether this combination has extra toxicity in a setting where electrolytes, CBC, and IV lines are not frequently monitored. Since the first trial of induction therapy is so critical to final success, the guideline for induction therapy with combination therapy is presently 2 weeks when practical. It would be helpful if clinical practice could replicate the clinical studies and implement the use of quantitative CSF yeast cultures of initial cultures then repeat an LP at 4-5 days to check if the patient has successful effective fungicidal activity (EFA) at 2 weeks, but EFAs in clinical practice have not been placed in any treatment guidelines yet. The use of 6 weeks combination therapy is generally reserved for patients with identified cryptococcomas or refractory features of treatment.

D. Liposomal amphotericin B and flucytosine should be continued for 2 weeks of induction therapy and then switched to consolidation phase with fluconazole 800 mg/d. This is the standard regimen if all goes well (or utilize the singled dose ambisome on a base of 2-week flucytosine and fluconazole). There are recommendations to obtain a CSF sample at the end of 1 or 2 weeks of treatment, and if it is culture positive, another induction course should be considered. Since, CrAg is not a good marker of success and quantitative CSF yeast counts are not routinely performed, stopping induction at 2 weeks is a clinical decision and hopefully most symptom/signs have resolved by then. During this 2-week period, patients can have sudden or progressive deterioration in their vision or hearing. This blindness is startling and may not be reversible. If

vision deterioration occurs, examine the patient for increased intracranial pressures, and if pressure is not a problem, then consider steroid treatment since the symptoms may be related to yeast and inflammatory cells in the vasculature of the optic nerve. However, this strategy has not been studied robustly.

E. Serum and CSF CrAg titers should be followed closely for first 10 weeks of therapy.
In the acute management of cryptococcal meningitis, the CrAg titers are not precise and are difficult to use to make management decisions, so they should not be followed serially[12]. At times in the CSF, a lowering titer may make one more confident in the diagnosis of IRIS, but a negative PCR is probably a better assessment for viable and/or poorly controlled yeast infection.

Correct answer: D.

Case Management

At the end of 2 weeks of liposomal amphotericin B and flucytosine, this patient was asymptomatic. The combination was stopped, and the patient received fluconazole 800 mg/d for 8 weeks. At the end of 5 weeks of antifungal therapy, his ART therapy was started with Biktarvy® (bictegravir, emtricitabine, tenofovir alafenamide). No problems were observed during those 10 weeks. In the first 2-6 months of therapy, there was close observation for the development of IRIS as manifested by new fevers, new intracranial findings, and/or worsening MRI scan of persistent or increasing leptomeningeal inflammation. No signs and/or symptoms occurred.

Challenge Question 5. At the end of 10 weeks of induction and consolidation therapy, what is the next management strategy?

A. Switch to suppressive therapy with fluconazole at 200-400 mg/d for a year and then consider stopping and follow closely
B. Stop all antifungal therapy at the end of 10 weeks and assume that ART-induced immunity will clear all residual yeasts
C. If CrAg titer has decreased and HIV load is negative with a CD4 count > 100 mm^3 at 12 weeks, then antifungal therapy should be stopped, and the patient should be followed without therapy every 3 months
D. The identification of cryptococcal species (eg, *C. neoformans* vs *C. gattii*) is important to make decisions regarding length of treatment

Discussion

A. Switch to suppressive therapy with fluconazole at 200-400 mg/d for a year and then consider stopping and follow closely. Since the risk of relapse is highest in the first year and immune reconstitution may take some time, the standard policy is to give suppressive therapy for 1 year. In the early pandemic with ART, this suppression was extended indefinitely. However, with potent ART, if the patient appears well and there is

some immune reconstitution and viral load suppression then fluconazole is stopped, and the patient is followed clinically after a year. There are a few studies containing a small number of participants which support this approach[31-32], and it has become routine practice. This approach is a part of guidelines and seems to be working well. As follow up, some clinicians will serially follow serum CrAg in unique circumstances and will respond to a significant elevation in CrAg titers or lowering of CD4 count < 100/µl with reinstitution of fluconazole-suppressive therapy.

B. Stop all antifungal therapy at the end of 10 weeks and assume that ART-induced immunity will clear all residual yeasts. There have been no studies in HIV-infected patients that suggests stopping therapy at 10 weeks because at present the cost-benefit ratio is simply too risky without positive data.

C. If CrAg titer has decreased and HIV load is negative with a CD4 count > 100 mm^3 at 12 weeks, then antifungal therapy should be stopped, and the patient should be followed without therapy every 3 months. Similar to **B**, even though the patient has improved by multiple parameters, there is currently no enthusiasm to truncate therapy in the first year post-CM diagnosis.

D. The identification of cryptococcal species (eg, *C. neoformans* vs *C. gattii*) is important to make decisions regarding length of treatment. Studies are exploring whether there are species or even specific isolate differences in outcome and if different treatments are required. Several large cohort studies[33,34] have tried to define differences in *C. neoformans* vs *C. gattii* management, but it is not yet apparent if these two species should be managed differently especially in HIV-infected individuals. Thus, recommendations remain the same for treatment (dose and duration) of disease with both species, so at present, species identification would not dictate management in cryptococcal meningitis in patients living with HIV infection.

Correct answer: A.

Case Continued

After the 10 weeks of induction and consolidation therapy, the patient was placed on fluconazole at 200 mg/d and was started on Biktarvy® (bictegravir, emtricitabine, tenofovir alafenamide), a potent single-daily-dose combination with no significant azole drug interaction at 5 weeks.

Challenge Question 6. During this suppression phase of treatment, the clinician should look out for which of the following clinical events?

A. Renewed headaches
B. New neurological signs such as unstable gait
C. Weight gain
D. Chapped lips and hair loss
E. Transaminase elevations

Discussion

A. Renewed headaches. Renewed headaches require an assessment to determine if they are related to: (1) relapsed infection, which is unlikely if there's been a good initial clinical response to induction and consolidation treatment and since development of a true stable azole-resistant strain is unlikely; (2) the development of IRIS, which can peak in its appearance around month 2-3 and is a more likely cause; (3) other non-infectious causes. Generally, the workup will require CT/MRI scan and LP to sort out the etiology if headaches persist.

B. New neurological signs such as unstable gait. New neurological signs such as increased intracranial pressure may be related to development of classic hydrocephalus, and re-neuro-imaging can define this occurrence and determine any need for shunting.

C. Weight gain. Weight gain may occur due to effective HIV treatment, and there is a feeling that Biktarvy® itself could add to this weight gain.

D. Chapped lips and hair loss. Chapped lips and alopecia are known common side effects of long-term azole exposure[35]. Reassurance that this is a side effect of medication and is reversible will be appreciated by the patient.

E. Transaminase elevations. Liver function abnormalities may be multifactorial. From a causal standpoint, the azoles are the most likely cause but other drugs may contribute. It is important for the clinician to decide what level to tolerate. Under 5X ULNs can be adjudicated at the bedside and higher levels may require close observation and the discontinuation or change of drug treatment.

Drug hepatitis may be caused by a specific drug or the entire drug class, and even drug levels may be correlated with hepatitis (eg, voriconazole)[36]. Therefore, it is not easy, but clinicians will need to deal with liver function testing at the bedside.

Correct answer: With ART therapies and the treatment of continuous azole compounds, the full year follow-up generally goes smoothly, but occasionally all of the signs or symptoms **(A-E)** may appear.

Case Outcome

This patient did very well, and the ulcerative lesion on his forehead resolved after 2-3 weeks of therapy with no other signs or symptoms. His fluconazole was stopped at 1 year of treatment, and he continued on his ART with negative viral load and CD4 count of 250 mm^3 and a serum CrAg 1:2.

Summary of Special Issues Regarding Cryptococcal Disease in HIV Patients

Acute mortality for cryptococcal disease in resource-available health care systems for HIV-infected individuals ranges from 5-15% and still runs around 50% in resource-limited health care systems, although in new clinical studies it appears to have improved to 25%. The morbidity and long-term costs of this infection are also high[37]. This case illustrates the complexity of initial and long-term management of cryptococcosis and cryptococcal meningitis as well as the potential morbidity and mortality if appropriate steps are not taken. Therefore, ordering an infectious diseases consultation and following clinical guidelines are important to address the nuances of care and improve outcomes for cryptococcosis and cryptococcal meningitis[38].

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