Opportunistic Infections in HIV-Infected Patients: Cryptococcal Meningitis

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Educational Objectives:

1. Describe the epidemiology and pathogenesis of cryptococcal infection in an HIV-infected patient.
2. Appreciate the signs and symptoms of disseminated cryptococcal infection.
3. Know the different phases of treatment for cryptococcal meningitis.
4. Understand when to initiate antiretroviral therapy for HIV/AIDs patients diagnosed with cryptococcal meningitis.

CASE ONE:

Mr CM is a 55-year-old man with history of HIV (not adherent on anti-retroviral therapy, last CD4 5 cells/uL, 5 years ago), presenting to the hospital with fever, headache, malaise, and rash for 2 weeks. His wife accompanies him and notes that he seems more confused than usual.

His vitals are T100.3F, heart rate 100 beats per minute, blood pressure 120/90, with 98% oxygen saturation on room air. He is lethargic. He has oral thrush. He has no focal neurologic deficits, but does have a molluscum-like rash on his lower extremities. His lungs are clear on auscultation.

He is found to have CD4 cell count of 5 cells/uL and viral load (VL) of 50,000 copies/mL.

Questions:

1. What is the differential diagnosis of meningitis in an advanced AIDS patient?

The differential diagnosis for a patient with meningeal symptoms and advanced AIDs includes fungal causes (cryptococcous, histoplasmosis, coccidiodes), parasitic (toxoplasmosis), bacterial (common bacterial agents as well as tuberculosis, Listeria, syphillus), and viral (HSV, VZV, CMV, primary HIV, EBV associated CNS lymphoma, JC virus associated progressive multifocal leukoencephalopathy).

2. What diagnostic studies would you order?

The patient requires a lumbar puncture. Prior to lumbar puncture, this patient should undergo neuroimaging. A study done by Hasbun and Quagilarello found that patients with immunocompromised state, abnormal level of consciousness, inability to answer two consecutive questions correctly, or follow two step command, abnormal visual fields, facial nerve palsy, aphasia had an abnormal CT head result (Hasbun et al, 2001). Because this patient has symptoms of altered mental status and is immunocompromised, he should undergo neuroimaging before lumbar puncture.

- Lumbar puncture studies should include opening pressure in the lateral decubitus position, cell count, gram stain, protein, glucose, and culture. CSF findings in cryptococcal meningitis include elevated protein, variable glucose (either normal or low), lymphocyte predominant pleocytosis, and yeast on gram or India ink stain. However, in patients with CD4 cell count less than 50 cells/uL, there is usually a lack of CSF pleocytosis. Up to 25% can have normal WBC in the CSF. Opening pressure is usually elevated (greater than 20cm H2O). CSF PCR studies for EBV, HSV, CMV, and HIV should be sent. Serum and CSF toxoplasma antibody studies should be sent.

- Diagnostic work up for suspected cryptococcal meningitis should also includes serum and cerebrospinal fluid (CSF) cryptococcal antigen (CrAg). The advantage of CrAg testing is that results are immediately available. The test can be performed by latex agglutination or by enzyme immunoassay. The CSF CrAg is both sensitive (93-100%) and specific (93-98%). Serum CrAg has similar sensitivity and specificity. The CrAg titer is reflective of shedding of the cryptococcal capsule.

- Routine blood cultures should also be sent in patients suspected of having cryptococcal meningitis. Up to two-thirds of blood cultures sent in HIV/AIDs patients with cryptococcal meningitis can be positive.

- The India ink stain on blood or CSF can also be performed, which will help identify the polysaccharide capsule of cryptococcus. This study however has low sensitivity.

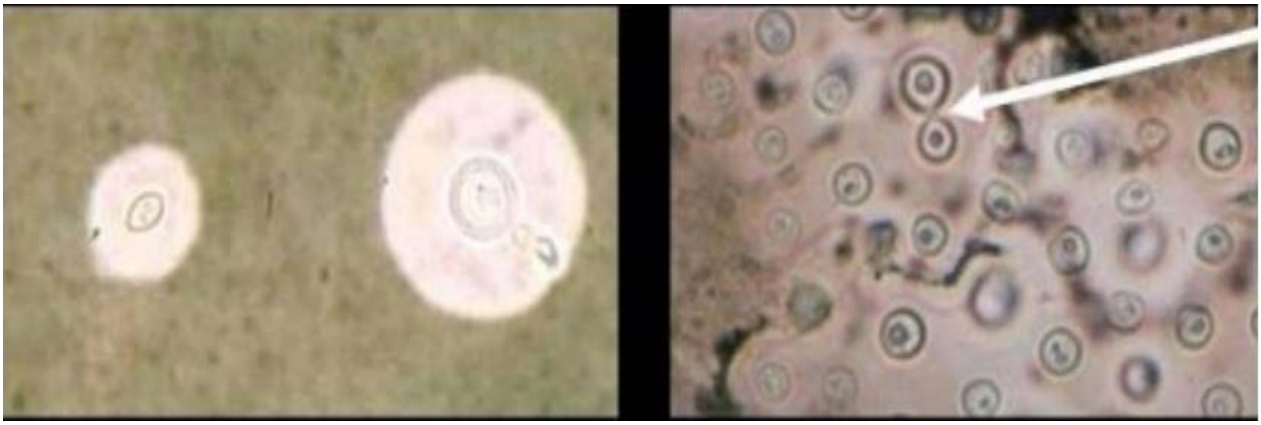

Figure 1. CSF fluid sample with C. neoformans on India ink stain. Budding yeast is indicated by the arrow.

CASE ONE CONTINUED:

Mr CM undergoes a CT scan of the head, which shows no mass lesions or herniation. He undergoes a lumbar puncture. He has an opening pressure of 30cm H_2O, CSF WBC is 10 cells/ul, glucose 10mg/dL, total protein 100mg/dL, with CSF CrAg titer of 1:1280.

3. What is the epidemiology of cryptococcal meningitis? What is the pathogenesis of cryptococcal meningitis?

Cases of cryptococcal meningitis are seen in patients with HIV/AIDS with CD4 count of less than 50 cell/uL. The introduction of anti-retroviral treatment and triazole-based antifungal therapy has decreased the incidence of cryptococcal meningitis, though incidence still remains high in resource limited countries. Globally, it is estimated about 1 million cases of HIV-associated cryptococcal disease occur annually.

Primary cryptoccocal infection occurs by inhalation, with initial site being pulmonary. Primary infection leads to fungemia which seeds in the meninges. This hypothesis is supported by a high prevalence of cryptococcal pneumonia in patients with cryptococcal meningitis on presentation. Cryptococcal infection in HIV-infected patients is caused by *Cryptococcal neoformans.*

4. What are the signs and symptoms that are associated with cryptococcal meningitis?

Patients with cryptococcal meningitis typically present with an indolent course of fever, headache, and malaise. Patients with disseminated cryptococcous in addition may present with cough, dyspnea and rash. On physical exam, patients may have confusion or lethargy. Cranial nerve palsies can be seen, which commonly include sixth cranial nerve palsy (abducens nerve). This occurs as a result of arachnoiditis, as inflammation from the infection settles down on the meninges that surround the cranial nerve nuclei (arachoid). In addition, as the nerve immerges near the bottom of the brain the sixth cranial nerve can be the first nerve to be compressed in the setting of increased intracranial pressure. Rash that is molluscum-like with central umbilication can be seen in disseminated cryptococcosis (Figure 1). Increased diastolic blood pressure may occur in setting of increased intracranial pressure.

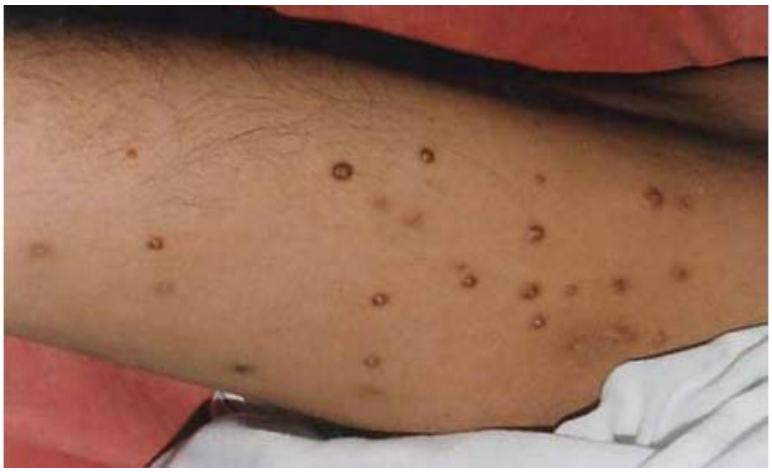

Figure 2. Patient with rash secondary to disseminated cryptococcosis. Note the molluscum-like characteristic of the rash.

5. **What are the poor prognostic signs for cryptococcal meningitis?**

A NEJM trial showed that pretreatment factors that predicted early death include any of the following (Saag et al, 1992):

- Abnormal mental status
- CSF CrAg >1:1024
- CSF WBC <20 cells per uL

6. How will you initially treat Mr CM? What type of side effects arise from treatment?

The Infectious Disease Society of America (IDSA) and Department of Health and Human Services (HHS) recommend treating HIV/AIDS patients with cryptococcal meningitis in three phases: 1) two-week induction phase 2) eight-week consolidation phase 3) extended maintenance phase (also known as secondary prophylaxis) (Table 1).

Table 1. IDSA Guidelines for Cryptococcal Menigitis. (Denotes strength of recommendation)

Stage of Therapy	Preferred Regimen	Alternative Regimens
Induction -For at least 2 weeks	Liposomal amphotericin B 3-4mg/kg/day IV plus Flucytosine 25mg/kg OI QID (AI)	Amphotericin B lipid complex 5mg/kg/day IV plus Flucytosine 25mg/kg PO QID (BII)
		Amphotericin B deoxycholate 0.7-1.0mg/kg/day IV plus Flucytosine 25mg/kg PO QID (AI)
		Liposomal amphotericin B 3-4mg/kg/day IV plus Fluconazole 800mg PO or IV daily (BIII)
		Amphotericin B deoxycholate 0.7-1.0mg/kg/day IV plus Fluconazole 800mg PO or IV daily (BI)
		Liposomal amphotericin B 3-4mg/kg/day IV alone (BIII)
		Fluconazole 800mg PO or IV daily plus Flucytosine 25mg/kg PO QID (BII)
		Fluconazole 1200mg PO or IV daily alone (CII)
Consolidation	Fluconazole 400mg PO or IV daily (AI)	Itraconazole 200mg PO BID (CI)

-For at least 8 weeks		
Maintenance Therapy -For at least 1 year	Fluconazole 200mg PO daily (AI)	

Adapted from Perfect et al. Clinical Practice Guidelines for the Management of Cryptococcal Disease: 2010 Update by the Infectious Disease Society of America. Clinical Infectious Disease 2010;50: 291-322.
Adapted from Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: Recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. http://aidsinfo.nih.gov/contentfiles/lvguideline s/adult_oi.pdf

The induction phase of treatment includes two weeks of amphotericin B (liposomal 3 to 4 mg/kg daily IV) with flucytosine (100mg/kg per day PO divided into four doses). Combination therapy with The goal of induction is to sterilize the CSF. A double blind multicenter randomized control trial in NEJM in 1997 (van der Horst et al, 1997) compared 321 patients with HIV/AIDS with first episode of crytococcal meningitis. The trial included two phases 1) First phase included treatment with high dose amphotericin B with or without flucytosine for two weeks, 2) Second phase is discussed below (see question 8). The study found CSF cultures were negative in 60% of patients who were receiving amphotericin B plus flucytosine vs 51% of patients receiving amphotericin B alone. The clinical outcome did not differ significantly. In addition, a randomized open label trial in Vietnam (Day et al, 2013) that compared amphotericin B monotherapy vs amphotericin B plus flucytosine showed fewer deaths and increased rates of CSF sterilization in the combination therapy group compared with monotherapy group.

Common side effects of amphotericin B include nephrotoxicity, electrolyte disturbance, anemia, and infusion site reactions.

The major side effects of flucytosine are neutropenia, anemia, and thrombocytopenia. Other side effects include gastrointestinal side effects as well as transaminitis.

CASE ONE CONTINUED:

Mr CM is started on amphotericin B and flucytosine and is treated for two weeks. He has multiple lumbar punctures performed over the course of two weeks due to severe headache. However, the lumbar puncture done at two weeks after therapy shows a CSF culture that is still positive for *C. neoformans.* He continues to have a severe headache, and his opening pressure from the last lumbar puncture is 30cm H_2O.

7. What is your next step in management? What is the role of glucocorticoid therapy?

Induction therapy should be extended until CSF cultures are sterilized, until opening pressure is less than 20cm H_2O and clinical improvement. The length of re-induction is guided by clinical and microbiological response. Of note, direct drug resistance of *C. neoforams* is extremely rare.

Increased opening pressure should be managed aggressively in patients with cryptococcal meningitis. Therapeutic lumbar punctures should be performed to reduce opening pressure to less

than 20 cmH_2O (if extremely high by 50% of initial opening pressure). The need of lumbar puncture is based on clinical symptoms, such as persistent headache or altered mental status.

There is no role for empiric glucocorticoids for the treatment of cryptococcal meningitis. This was illustrated in a multi-site randomized control trial on patients with HIV-associated cryptococcal meningitis (Beardsley et al, 2016). About four hundred patients were randomized to either dexamethasone or placebo for three weeks in combination with amphotericin B and fluconazole. The study was stopped as the mortality was higher in the dexamethasone group compared the placebo group at 10 weeks. In addition, patients in the dexamethasone group had higher rates of disability and slower rate of fungal clearance from CSF.

CASE ONE CONTINUED:

After an additional week of amphotericin B and flucytosine, Mr CM states his headache is improving. His repeat lumbar puncture shows no growth to date.

8. What is your next step in management? When should you start antiretroviral treatment for Mr CM?

Mr CM should be started on consolidation therapy for at least 8 weeks. IDSA guidelines recommend treating with fluconazole 400mg PO once daily for minimum of 8 weeks. In the NEJM study done by van der Horst et al in 1997 noted above, following the first phase of treatment, the second phase of the trial included a comparison of 8 weeks of fluconazole versus itraconazole. Among patients who underwent repeat lumbar puncture at the end of the sterilization phase, 97% of the fluconazole arm had negative CSF culture compared to 92% of itraconazole arm. Clinical outcomes were similar in both arms. Thus, fluconazole is the preferred regimen of choice for consolidation therapy, but itraconazole is thought to be an acceptable alternative.

After 8 weeks of consolidation therapy, patient should be switched to maintenance therapy, which consists of fluconazole 200mg PO daily.

The timing of antiretroviral therapy must be weighed between the risks of immune reconstitution inflammatory syndrome (IRIS) and the benefit of immune recovery. A randomized control trial done in Uganda and South Africa on HIV patients on the treatment for cryptococcal meningitis showed that delayed ARV initiation had significantly improved survival (Boulware 2014). In this trial, HIV-infected patients with cryptococcal meningitis who had never been on ARVs were assigned to early ART initiation (1-2 weeks after diagnosis) versus delayed ARV initiation (5 weeks after diagnosis). The 26-week mortality with early ART initiation was 45% compared with delayed ARV of 30%. Thus, delayed ARV initiation is recommended in patients presenting with cryptococcal meningitis.

CASE ONE CONTINUED:

One and a half years later you see Mr CM in clinic for follow up. He is on a stable antiretroviral therapy and has been on antifungal therapy for 1.5 years. His repeat CD4 was 120 cells/uL four months ago, and today it is 145 cells/uL. VL has been undetectable (UD) for 6 months.

9. What are the criteria to discontinue cryptococcal meningitis maintenance therapy? Are there any additional laboratory studies warranted?

Maintenance therapy can be discontinued when all following criteria are met on patients with 1) at least 1 year of antifungal treatment 2) on antiretroviral therapy with CD4 cell count >100 cells/uL and VL is undetectable for >3 months. There are no current guidelines for the frequency and duration of checking serum CrAg. Some authors recommend checking CrAg at the end of maintenance therapy, then checking every 3 months until CD4 count is 200 cells/uL.

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