A Case of Cryptococcal Meningitis

History

- Patient transferred from Columbia Memorial Hospital with lethargy, shortness of breath, chest pains and failure to thrive.
- HIV was newly diagnosed there
  - CD4 4 cells/cmm
  - VL 33,000 copies/mL
- Transferred with:
  - 1. Pancytopenia.
  - 2. Splenomegaly.
  - 3. Coagulopathy with elevated bilirubin and INR, and very low serum albumin.
  - 4. She was also found, later during her hospital stay there, to have non-anion gap metabolic acidosis, with a normal serum creatinine of 0.6 to 0.8 mg/dL.
  - 5. Positive serum cryptococcal antigen
Social History

- Never used drugs; former smoker.
- Married 23 years
  - No extramarital relations reported
  - Husband tested HIV negative
- One son, age 22
  - Donated blood on several occasions, and was never contacted by Red Cross
- Two former partners, with whom she had lost contact

12/18/12 Admission Physical Exam

- Temp 37C; Tmax 39C; P 89; BP 100/58; R 20; Pulse oximetry 97% on room air.
- General: Chronically ill appearing
- Pharynx clear; mildly icteric sclerae
- Chest clear
- Cardiac: Regular rate and rhythm, with SEM
- Abdomen: Hepatosplenomegaly
- Extremities: No edema
### Labs

- WBC 1300 with 40% segs and 40% lymphs
- Hgb 9.5 g/dL; Hct 27%; Plts 44K
- Na+ 131; K+ 3.8’ Cl- 101; HCO3 14
- BUN 5; Creatinine 0.8 mg/dL
- Alb 1.3 g/dL; Bilirubin 1.4 mg/dL; ALT 26 IU/L
- PT 15.6; PTT 53 seconds
- Hepatitis C Ab +; PCR +
- Urinalysis 4.0 urobilinogen; no protein.
- ABG: 7.45/pCO2 19/ pO2 75/ HCO3 13/ 94% RA

### CSF and Micro Results

- Opening pressure 27 cm; CP 17 cm; OP 1 wk later 18
- Positive CSF CRAG 1:100
- Gram stain negative
- 82 WBCs/hpf; 0 RBCs; 76% lymphs, 20% monos; 2% polys
- Glucose 37 mg/dL; Protein 81 mg/dL
- CSF culture positive for *C. neoformans*
- Blood culture positive for *C. neoformans*
- Bone marrow with yeast forms (from Columbia Memorial)
Hospital Course

- Received 2 weeks of liposomal Ampho B
- 5-FC not used due to pancytopenia
- Fluconazole used concomitantly 400 mg daily (initially given 800 mg daily)
- Creatinine peaked at 2.1 mg/dL
- Bilirubin slowly rose to 22 mg/dL
  - Deeply jaundiced
  - PT 18.6 seconds
  - ALT 32 IU/L
  - Creatinine 1.3 mg/dL

HIV OI Treatment Guidelines

- The addition of flucytosine to amphotericin B during acute treatment is associated with more rapid sterilization of CSF (595,596). The combination of amphotericin B deoxycholate with fluconazole, 400 mg daily (BII), is inferior to amphotericin B combined with flucytosine for clearing Cryptococcus from CSF, but is more effective than amphotericin B alone (BII) (597).

MMWR Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents April 2009.
**Concomitant Meds**

- Atovaquone for PJP prophylaxis
- Azithromycin for MAC prophylaxis started, and held after bilirubin started rising
- Valacyclovir for positive HSV PCR from tongue ulcer
- Esomeprazole for GI prophylaxis
- Darbepoetin for anemia of chronic disease
- Spironolactone 50 mg daily for cirrhosis, hypokalemia and edema
- Folate, potassium, magnesium and bicarbonate replaced
- HAART not yet started due to risk for IRIS, and now bilirubin problem

**Imaging**

- Head CT negative
- CXR negative
- No obstruction by hepatic ultrasound
  - Small, nodular liver with splenomegaly
  - HIDA scan not helpful due to cirrhosis
COAT: Early vs Delayed ART in Tx-Naive Pts With Cryptococcal Meningitis

- Optimal timing of ART initiation after diagnosis of CM remains uncertain
  - Early ART associated with increased mortality in recent trials in resource-limited settings\(^1,2\)
  - Earlier study showed improved outcomes with immediate vs delayed ART during acute OIs\(^3\)

- COAT study compared 26-wk survival in tx-naive pts with first episode of CM who received early vs deferred ART initiation\(^4\)

Stratified by treatment site and mental status (altered vs not)

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<thead>
<tr>
<th></th>
<th>Early ART Initiation</th>
<th>Deferred ART Initiation</th>
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<tbody>
<tr>
<td>ART started</td>
<td>&lt; 48 hrs after study entry, before hospital discharge (n = 88)</td>
<td>≥ 4 wks after study entry, after hospital discharge (outpatient) (n = 89)</td>
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COAT: Increased Mortality With Early ART During CM Induction Therapy

- Significantly lower 6-mo OS with early vs deferred ART\(^1\)
  - Enrollment halted early by NIAID Africa DSMB

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<thead>
<tr>
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<th>Deferred ART</th>
<th>Early ART</th>
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<tbody>
<tr>
<td>OS</td>
<td>70%</td>
<td>55%</td>
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<td>P</td>
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- Mortality associated with
  - Altered mental status at study entry (Glasgow Coma Scale score < 15; OR: 3.0; P = .05)
  - Patients with CSF WBC counts < 5 cells/mm\(^3\) at randomization (HR: 3.3; P = .01)

- In separate analysis of COAT data, reduced interferon gamma secretion associated with increased risk of IRIS or death\(^2\)
  - Multivariate analysis of death or CM-IRIS risk: OR per 2-fold increase 0.806 (95% CI: 0.684-0.958; P = .014)

Points to Remember

1) Consider Cryptococcus in the differential diagnosis of patients with CD4 < 200 cell/cmm, and FUO, failure to thrive, or headache.

2) 5-Flucytosine plus Amphotericin B associated with more rapid CSF clearing, though not all patients will be able to tolerate it.

3) HAART should probably be delayed by 4 or more weeks after the diagnosis of Cryptococcal infection.

Other References


