Recurrent meningitis after ART initiation in 2 patients known with cryptococcal meningitis

Graeme Meintjes
University of Cape Town
Case 1

• 23 year old woman
• Known HIV infection, CD4 = 37, but ART-naïve
• Presented 7 March 2012
  – Headaches, weakness, dizziness x 2 weeks
  – LOW and cough x 3 months
• Febrile, GCS=15, no meningism, no focal neurology
• Opening pressure=7cm H₂O
• CSF
  – Poly= 0  Lymph=1
  – Protein=0.42  Glucose=2.4
  – Indian ink and CrAg positive
  – Cryptococcal culture: moderate growth
• Investigations for TB all negative
Initial management

• AmB 1mg/kg/d + Fluconazole 800mg/d x 14d
  – Hb 9.1 -> 7.1 then transfused 2 units
  – Creat = 67 on admission
  – Creat = 179 on Day 13, given additional fluids
  – Creat = 139 on discharge and later normalised
  – Asymptomatic on discharge

• Started ART while in hospital, 9d after admission
  – Early arm COAT trial
Multiple repeat presentations

• 2 weeks later
  – Headache x 1 d
  – Adherent to ART and fluconazole
  – 2 lumbar punctures 3 days apart
    • Opening pressure: not measured then 7cm H\(_2\)O
    • No cells
    • Protein = 0.24
    • Culture negative
  – Discharged asymptomatic
• 5 days later
  – Headaches, nausea, vomiting & dizziness for 1d
  – LP
    • OP 67cm H₂O, drained 25ml, closing pressure 14cm H₂O
    • Still non-inflammatory and culture negative
• What do you think diagnosis is?
Management

– Started on Prednisone 1mg/kg/d for C-IRIS
– Initially OP remained > 50 cm H$_2$O
– Symptoms resolved
• Prednisone dose
  – After 3 weeks reduced to 30mg/d
  – Then 1 week later 15mg/d
• Headache and dizziness recurred
  – LP: high opening pressure again
  – Increased dose to 60mg/d, weaned over 6 weeks
• 3 weeks after prednisone stopped
  – Recurrent symptoms
  – Another course of prednisone weaned over 10 weeks
• After this asymptomatic and well

• She had LPs 2-3x per week when symptomatic
• Opening pressure always > 40cm H₂O
• But symptoms resolved with prednisone and therapeutic LPs
• All CSF analyses non-inflammatory and culture negative
• CT head showed no hydrocephalus and no mass lesion

• 1 year on ART
  – Well
  – CD4 = 254
  – VL = 100 copies/ml
Key issues

• Prolonged IRIS

• Steroid responsive

• IRIS usually associated with CSF pleocytosis, but not always
Case 2

- 31 year old man
- CD4 = 114
- PTB in 1996
- Presented in July 2012
  - History of severe headache and confusion and GCS = 8/15
  - Lumbar puncture
    - OP= 27cm $H_2O$
    - Poly=3 Lymph=11  Protein=1.78  Glucose=3.5
    - Indian ink and CrAg positive
  - Responded to AmB/Fluconazole 800mg daily
  - 2 LPs, normal opening pressures
  - GCS normal and CSF sterile by Day 7
  - Discharged after 2 weeks
• Started ART 2 weeks after discharge
  – TDF, 3TC, Efavirenz

• After 2 weeks on ART
  – Headache, neck pain, blurred vision
  – LP
    • OP=16 cm H$_2$O
    • Poly=0  Lymph=25  Protein=1.48  Glucose=2.8
    • Culture negative
  – Resolved with analgesia
• Re-presented 12 weeks on ART
  – Confusion with GCS=13
  – No history provided
  – No focal neurology, no meningism

• LP
  – OP=28 cm H₂O
  – Poly=0  Lymph=75  Protein=3.96  Gluc=1.4,
  – Indian ink and CrAg negative
  – Later culture negative

• Features of SIADH
  – Na = 114  (K and renal function normal)
  – Urine osmolality=471 and plasma osmolality=244
  – Urine Na = 101

• Viral load < 40 copies/ml
• What do you think diagnosis is?
CM diagnosis
July 2012

Representation now
12 weeks on ART

Obstructive hydrocephalus and cerebral venous sinus thrombosis
Management

- Dexamethasone 4mg 8 hrly x 10 days then Prednisone 60mg/day to treat C-IRIS
- Fluid restriction for SIADH
- Enoxaparin then Warfarin for CVST
- AmB x 1 day then fluconazole 600mg/daily
- TB treatment
Further results

- CSF TB culture positive after 13 days
  - MTB sensitive to Rif and INH

- Full recovery on TB treatment and weaning dose of steroids
Pointers to TBM in this case

• SIADH
• CT Head
  – Obstructive hydrocephalus
  – CVST
• CSF protein = 3.96

• Considerable overlap with CM-IRIS in presentation

• Does not mean every case of CM-IRIS should be treated for TBM, but be vigilant
1737 cases with markedly abnormal CSF cell counts, biochemistry and/or microbiological diagnoses

8 Patients had CM and TBM co-infection
Symptomatic relapse of HIV-associated cryptococcal meningitis in South Africa: The role of inadequate secondary prophylaxis

Joseph N Jarvis, Graeme Meintjes, Zomzi Williams, Kevin Rebe, Thomas S Harrison

Fig. 1. Causes of symptomatic relapse of cryptococcal meningitis, divided into immune reconstitution inflammatory syndrome (IRIS) in patients taking ART, absence of fluconazole secondary prophylaxis (subdivided into patient non-adherence and not given – either not prescribed, not dispensed, or not continued at primary care level), and relapses in patients taking fluconazole prior to starting ART.
Paradoxical cryptococcal meningitis IRIS

74% of reported cases have this as sole or dominant feature

Patient diagnosed with CM
Started on treatment and improves

Starts ART

Recurrent meningitis/neurologic symptoms
CSF pleocytosis
Typically fungal culture negative
Raised intracranial pressure

Haddow, Lancet ID 2010
CM-IRIS management

• Consider and exclude alternative diagnoses
  – Fluconazole non-adherence
  – Other causes of meningitis

• Lumbar puncture
  – Opening pressure
  – Therapeutic CSF drainage (often repeated taps required)
  – CSF culture

• Intensify antifungal treatment awaiting culture result

• Continue ART

• In severe or refractory cases, particularly once culture confirmed to negative
  – Corticosteroids (Prednisone 1mg/kg, anecdotal evidence)
Acknowledgements

• James Scriven
• Charlotte Schutz