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

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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 H_2O
- 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_2O
    - No cells
    - Protein = 0.24
    - Culture negative
  - Discharged asymptomatic

- 5 days later
  - Headaches, nausea, vomiting & dizziness for 1d
  - LP
    - OP 67cm H_2O, drained 25ml, closing pressure 14cm H_2O
    - Still non-inflammatory and culture negative

- What do you think diagnosis is?

Managment

- Started on Prednisone 1mg/kg/d for C-IRIS
- Initially OP remained > 50 cm H_2O
- 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 H_2O
- 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

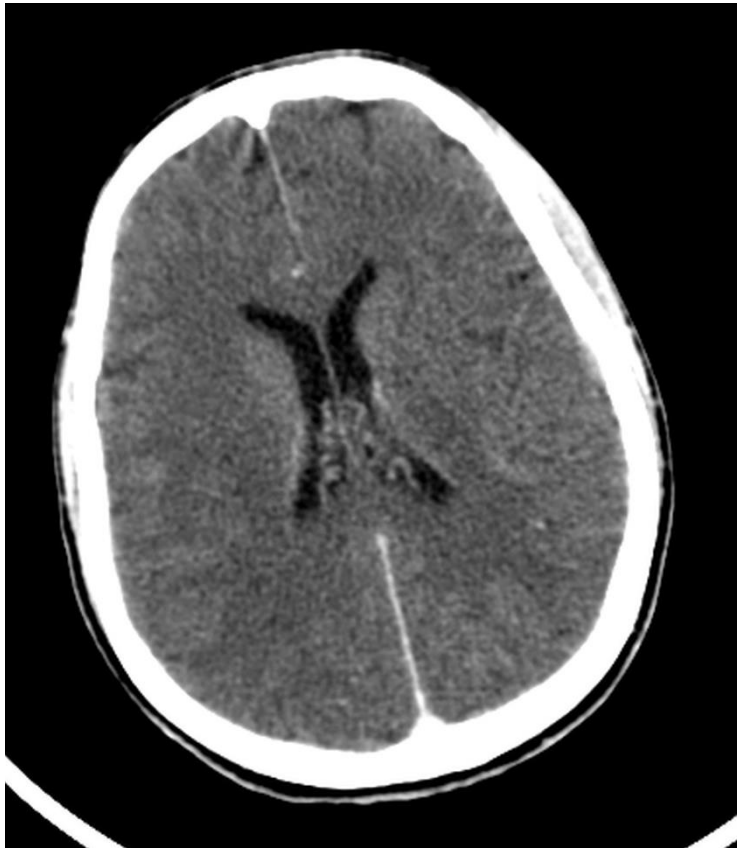
- 31 year old man
- CD4 = 114
- PTB in 1996
- Presented in July 2012
  - History of severe headache and confusion and GCS = 8/15
  - Lumbar puncture
    - OP= 27cm H_2O
    - Poly=3 Lymph=11 Protein=1.78 Glucose=3.5
    - Indian ink and CrAg positive
  - Responded to AmB/Fluconazole 800mg daily
  - 2 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

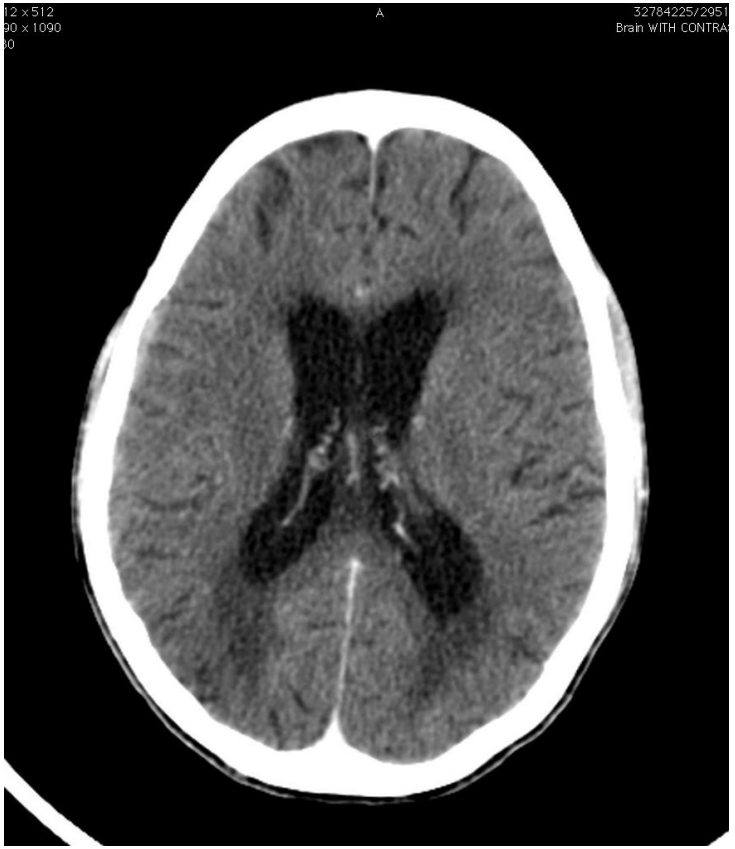
- After 2 weeks on ART
  - Headache, neck pain, blurred vision
  - LP
    - OP=16 cm H_2O
    - Poly=0 Lymph=25 Protein=1.48 Glucose=2.8
    - Culture negative
  - Resolved with analgesia

- Re-presented 12 weeks on ART
  - Confusion with GCS=13
  - No history provided
  - No focal neurology, no meningism
- LP
  - OP=28 cm H_2O
  - 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

Jarvis *et al. BMC Infectious Diseases* 2010, **10**:67
http://www.biomedcentral.com/1471-2334/10/67

BMC
Infectious Diseases

RESEARCH ARTICLE Open Access

Adult meningitis in a setting of high HIV and TB prevalence: findings from 4961 suspected cases

Joseph N Jarvis[1,2,3,4*], Graeme Meintjes[1,4,5], Anthony Williams[1], Yolande Brown[1], Tom Crede[1], Thomas S Harrison[3]

- 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

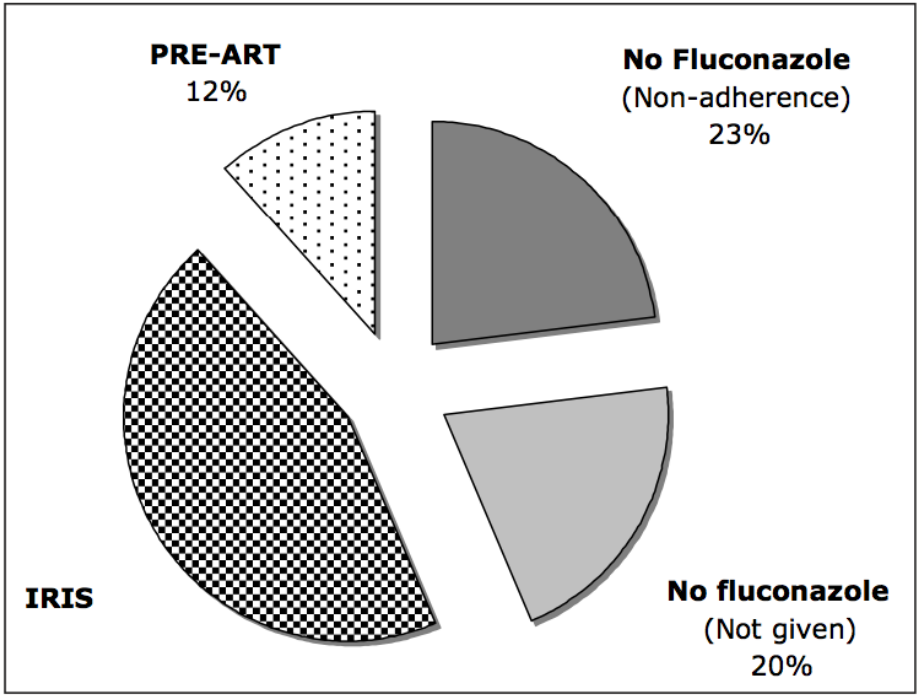


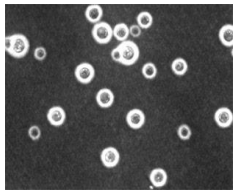
Fig. 1. Causes of symptomatic relapse of cryptococcal meningitis, divided into immune reconstitution inflammatory syndrome (IRIS) in patients taking ART, absence of fluconazole secondary prophylaxis (subdivided into patient non-adherence and not given – either not prescribed, not dispensed, or not continued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

Jarvis, SAMJ 2010

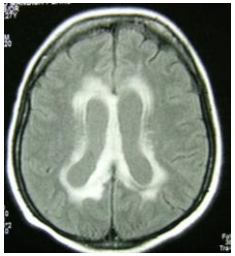
Paradoxical cryptococcal meningitis IRIS

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)

SA HIV Clin Soc Guidelines 2013
Longley, Curr Opin Infect Dis 2013

Acknowledgements

- James Scriven
- Charlotte Schutz