A CRYPTIC DIAGNOSIS

OLIVER KOCH

Oxford University Hospitals

NHS Trust

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BACKGROUND

- 50 year old male
- End-stage renal failure secondary to type 2 diabetes mellitus, hypertension
- Cadaveric kidney transplant

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HISTORY

- Re-admitted 2 months post transplant
- Worsening headaches for last 2 weeks
- 5 days of nausea & vomiting
- Increasing confusion
- Photophobia
- Recent intermittent unilateral facial numbness, dysmetria, dysdiadochokinesis

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DRUG HISTORY

- At transplant: Basiliximab (IL2α-blocker of activated T-cells)
- on re-admission:
  - Tacrolimus 6mg twice daily
  - Mycophenolate mofetil 540mg twice daily
  - Prednisolone 5mg once daily
  - co-trimoxazole, aspirin, atorvastatin, Glargine, gliclazide

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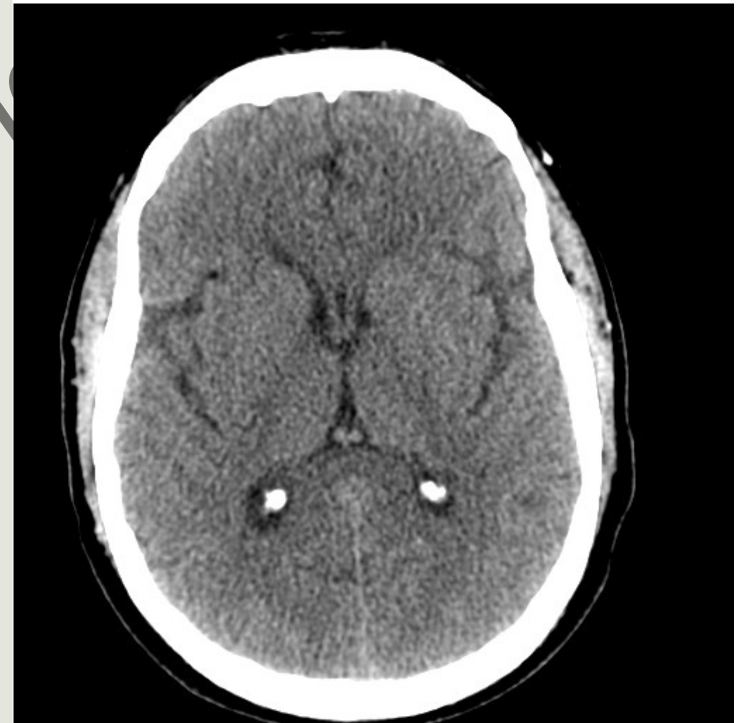
CT HEAD

*"....reduced extra axial space for the patient's age, particularly at the vertex and in the temporal lobes where there is some sulcal effacement....**Appearances suspicious for raised intracranial pressure**. No definite cause identified....."*



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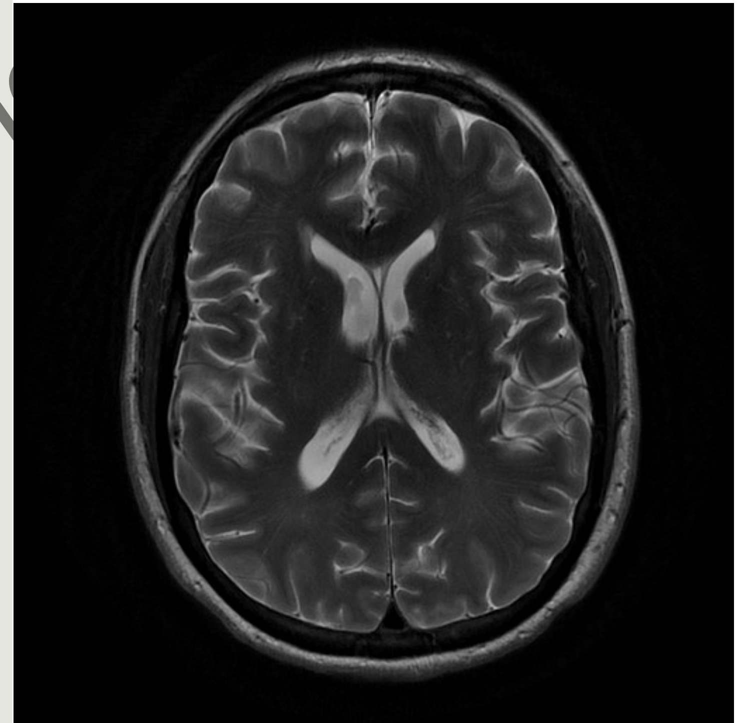
MRI / MRV BRAIN

*" …**mild cortical swelling over the right hemisphere with narrowing of the sulci and increased cortical signal** in the T2-weighted images…**no white matter lesions**…peri-optic CSF spaces are distended. There is no other sign of impaired CSF flow. There is no hydrocephalus…no occlusion of cerebral venous structures..."*



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LUMBAR PUNCTURE

- Opening pressure unrecordable (>40cm H_2O)
- WBC 44/µl (Polymorphs 44/µl)
- CSF protein 1262 mg/L; CSF glucose 3.1mmol/l (blood glucose not done)

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ADDITIONAL INFORMATION

- One week post transplant post-mortem of donor had revealed diagnosis of Cryptococcal meningitis (HIV neg).
- Recipient had been well at that point, no treatment or prophylaxis given

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- Opening pressure unrecordable (>40cm H_2O)
- WBC 44/µl (Polymorphs 44/µl)
- CSF protein 1262 mg/L; CSF glucose 3.1mmol/l (blood glucose not done)
- CrAg & India Ink positive
- CSF Culture: ***Cryptococcus neoformans var grubii***
  - Species of donor and recipient identical as per microsatellite / copy number variation typing
  - Sensitivities: Amphotericin sensitive, Flucytosine intermediate, Fluconazole intermediate, Voriconazole sensitive

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MANAGEMENT

- Ambisome 3mg/kg once daily & Flucytosine 50mg/kg twice daily
- 2 weeks induction therapy followed by Fluconazole consolidation (400mg) / maintenance (200mg) therapy
- Regular LPs to reduce pressures to <20cm H_2O
- Symptoms resolving; discharged home

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But 9 months later…

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HISTORY

- 5 days of headaches, auditory hypersensitivity, vomiting
- One episode of fever at 38.5° C
- Neurological examination normal

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DRUG HISTORY

- Immunosuppression:
  - Mycophenolate mofetil stopped 7 months earlier secondary to CMV viraemia
  - Tacrolimus 1mg twice daily (dose reduced 6 months ago as worsening renal function secondary to calcineurin inhibitor toxicity (as per biopsy)
  - Prednisolone 5mg once daily
- remains on Fluconazole maintenance therapy (200mg once daily)

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INVESTIGATIONS

- WCC 7.6 x10^9/l, CRP 34 mg/L
- Creatinine 145 µmol/L
- Toxo IgM/IgG neg.; HIV neg.
- CT head: no abnormality detected

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LUMBAR PUNCTURE

- Opening pressure 33cm H_2O
- WBC 28/µl (Polymorphs 6/µl, Lymphocytes 22/µl), RBC 74/µl
- CSF Protein 684mg/L; CSF Glucose 3.8mmol/l (blood glucose not done)
- Gram stain neg., India ink neg.

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LUMBAR PUNCTURE

- Opening pressure 33cm H_2O
- WBC 28/µl (Polymorphs 6/µl, Lymphocytes 22/µl), RBC 74/µl
- Protein 684mg/L; CSF Glucose 3.8mmol/l (blood glucose not done)
- Gram stain neg.; India ink neg.
- no bacterial growth; mycobacterial and fungal cultures awaited
- PCR negative for HSV-1, HSV-2, VZV, enterovirus
- CSF CrAg positive (1:20), Serum CrAg positive (1:320)
- CSF Cytospin: "*…lymphocytic pleocytosis…no malignant cells…*"

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MANAGEMENT

- Ambisome 3mg/kg once daily & Flucytosine 50mg/kg twice daily
- Ceftriaxone 2g twice daily – stopped after no growth from CSF at day 3

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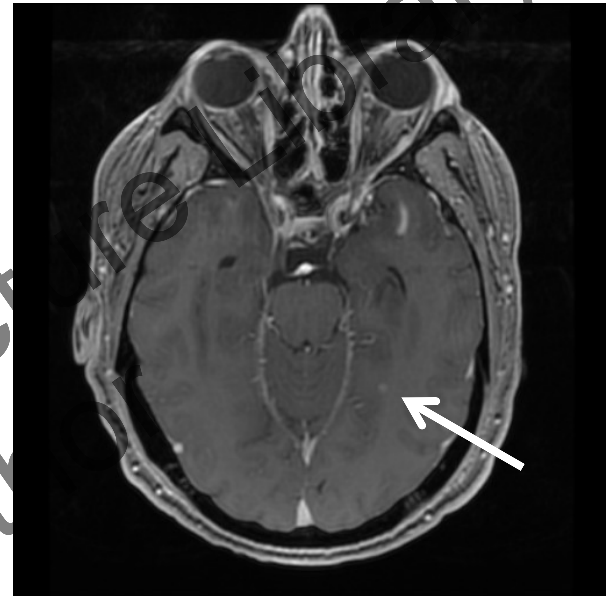
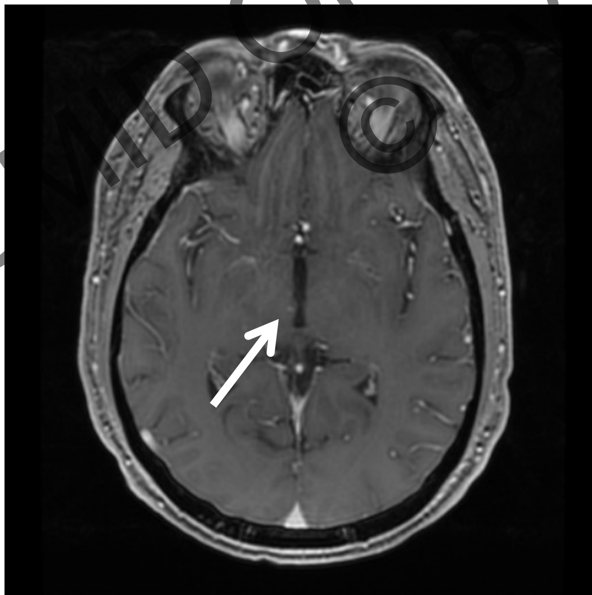
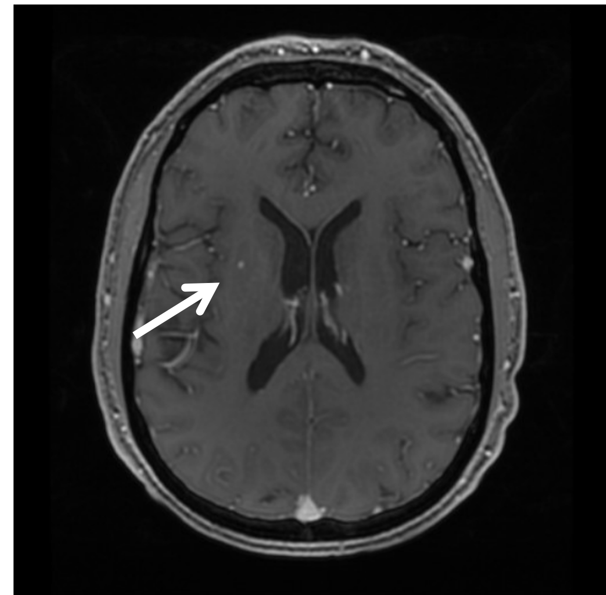
MRI

"…At least 3 tiny nodules of parenchymal contrast enhancement in the right putamen, right thalamus and left posterior lobe…"







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FURTHER MANAGEMENT

- Nodules demonstrated on MRI deemed to small for biopsy
- Serial LPs to lower CSF pressures; cell counts remained high
- Following 2 week induction therapy switched to Voriconazole consolidation therapy
- 7 days later c/o nausea & vomiting; Tacrolimus levels markedly raised

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FURTHER MANAGEMENT

- Voriconazole consolidation therapy switched to Fluconazole (400mg) in view of high Tacrolimus level
- CSF mycobacterial and fungal cultures remained negative
- After 3 weeks patient clinically improved & discharged home; remains well at 6 months follow up
- Repeat MRI at follow up reported as normal

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DIAGNOSTIC CONUNDRUM

- Relapsing Cryptococcal meningitis?
  - **Con:** No growth from CSF, CrAg CSF titres low, CrAg test can stay significantly positive for several months after successful therapy (Hongzhou, J. Clin. Microbiol. 2005)

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- Immune Reconstitution Syndrome?
  - **Con:** Diagnosis of exclusion, no other systemic features; low incidence?

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- Immune Reconstitution Syndrome?
  - **Con:** Diagnosis of exclusion, no other systemic features; low incidence?
- Other Pathology (e.g. TB, CNS lymphoma)?
  - **Con:** TB cultures neg.; cytospin neg for malignancy; patient recovered without interventions other than regular LPs and antifungals

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SUGGESTED DIAGNOSIS

Immune reconstitution inflammatory syndrome mimicking relapsing cryptococcal meningitis in a renal transplant recipient

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LEARNING POINTS

- *Cryptococcus neoformans* can be transmitted by solid organ transplantation (Baddley, CID. 2011).
- CrAg can stay significantly positive for several months even after successful therapy (Hongzhou, Clin Microbiol. 2005).
- Immune reconstitution inflammatory syndrome can mimic relapsing cryptococcal meningitis in transplant recipients (Legris, Transpl Infect Dis. 2010; Crespo, Liver Transpl. 2008).

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