# HLH, CNS histoplasmosis and a catalogue of opportunistic infections

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## Presentation & First Weeks

A previously well **25-year-old male** arrived to the UK from West Africa in Autumn 2025. Presenting to his local hospital a few weeks later he reports a 2-month history of **sore throat, worsening shortness of breath, and 18kg of unintended weight loss**. He weighs 33kg at the time of initial presentation. Blood-borne virus screening at admission is positive for HIV and his **CD4 cell count is <35 cells/mm$^3$.** Severe *Pneumocystis jirovecii* pneumonia is diagnosed based on raised Beta D Glucan of >500 and CT Thorax appearances and he is commenced on treatment with IV co-trimoxazole and steroids. Admitted to ICU for ionotropic support and commenced on treatment for neutropaenic sepsis, this patient experiences a very turbulent course including EBV and CMV viraemia prompting valganciclovir treatment**. Empiric *Mycobacterium avium intracellulare*** treatment with rifabutin, ethambutol, moxifloxacin, and azithromycin is started with two blood cultures subsequently positive for MAI.

Other issues encountered in these initial weeks after presentation include hyperkalaemia (co-trimoxazole->atovaquone), acute kidney injury, large volume melaena, cryptosporidiosis with bowel failure requiring parenteral nutrition, acute liver injury, rising ferritin, and dropping cell counts. HLH is suspected with a **H-Score of 188 (80% probability of HLH).** Discussion with the UCLH HLH MDT results in transfer to UCLH for further investigation and treatment. Anakinra and steroids are commenced with good effect.

## CNS Histoplasmosis

After transfer to UCLH, this patient is noted to have a GCS of 9 (E4V1M4). CNS imaging is difficult to achieve with multiple incomplete studies due to patient movement. An unenhanced MRI Head in November revealed **numerous cortical and subcortical hyperintensities** of the frontal, parietal, right temporal, and left occipital lobes. Further investigations are summarised below (Table 1 & 2, Figure 1 – 4).

| Test | Result | Date |
|---|---|---|
| Histoplasma immunodiffusion | Negative | 11/11 |
| Histoplasma Urine Antigen | Positive | 13/11 |
| Beta D Glucan | Positive (>500) | 14/11 |
| Yeast blood PCR | Negative | 17/11 |
| Galactomannan ELISA | Positive | 17/11 |

**Table 1.** Fungal investigation results supporting disseminated histoplasmosis diagnosis

| Test | Result |
|---|---|
| HIV viral load | Undetectable |
| Histoplasma antigen (CSF) | Detected |
| Fungal Culture | Negative (21 days) |
| JC virus | Not detected |
| Cryptococcal antigen | Negative |
| Viral PCR panel | Negative |
| Toxoplasma Antibody/PCR/Dye test | Negative |
| Cell counts | Clotted – not resulted |
| Gram stain | No organisms seen |
| Toxoplasma Antibodies/Dye test | Negative |
| CSF Protein | 0.24 g/L |
| CSF Glucose | 2.9 mmol/L |

**Table 2.** CSF interrogation. Results from CSF obtained from lumbar puncture performed on two occasions 2nd and 3rd week of November 2025.

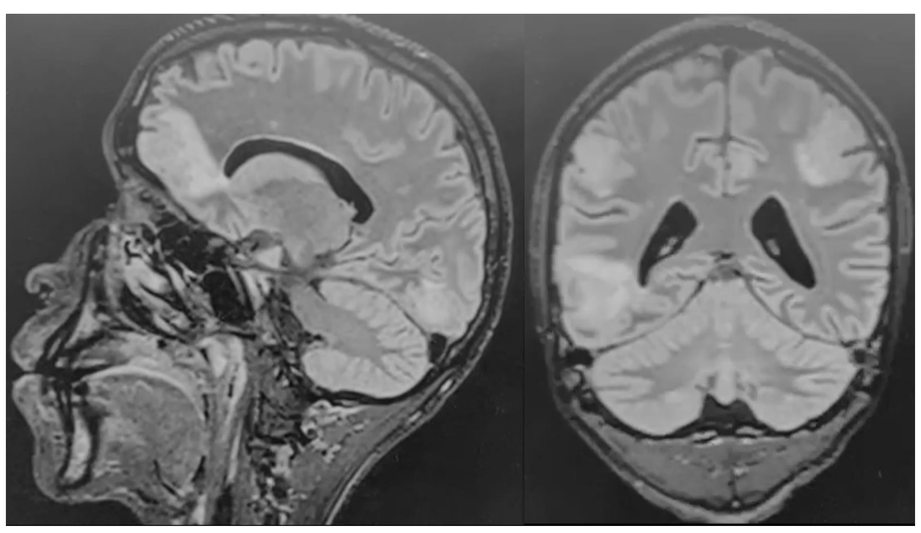


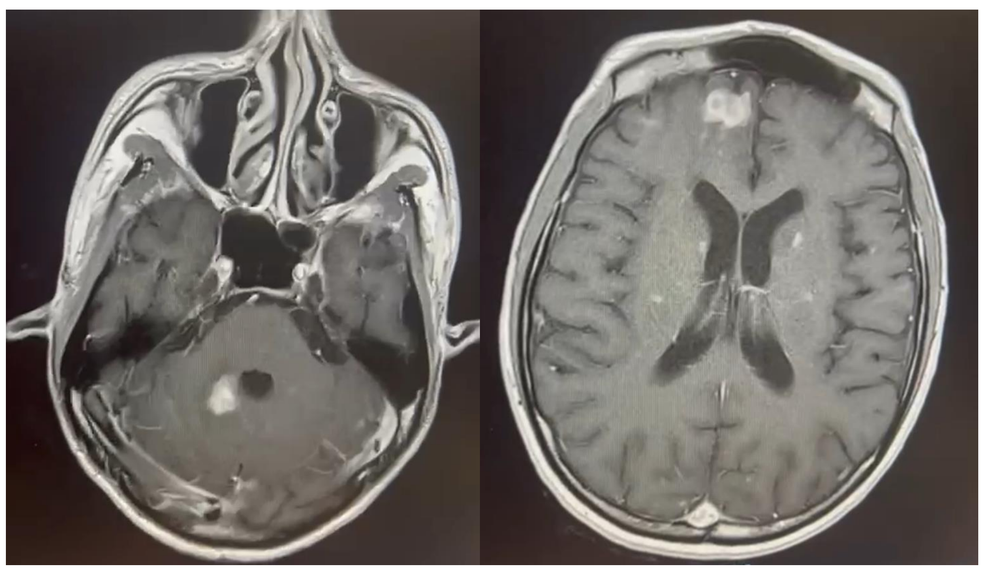
**Figure 1 & 2.** Images from unenhanced MRI head December 2025 showing multiple lesions affecting the frontal, parietal, and temporal lobes.

## Clinical Course

Treatment is commenced for CNS histoplasmosis initially with **liposomal amphotericin B** 3mg/kg subsequently escalated to 5mg/kg with little clinical improvement evident . Following six weeks of IV LAmB, this patient is transitioned to oral posaconazole, however, difficulty achieving adequate drug levels is encountered for this and each subsequent oral azole drug trialed **(posaconazole->itraconazole->voriconazole).** After intensification with amikacin for four weeks the MAI treatment is rationalised to azithromycin and ethambutol because of concerns about drug interactions with rifabutin. However, **drug levels remain subtherapeutic and IV LAmB was restarted**. In early January 2026, seizures developed which are effectively managed with levetiracetam. Little improvement in the abulic phenotype is observed despite treatment. Intermittent periods of pyrexia are encountered and treatment with meropenem is given for urosepsis.

Interval brain imaging is performed in March 2026 which reveals **new cerebellar lesions** (right>left) while previously seen lesions show improvement. Concern for a separate pathology **prompts empiric treatment for cerebral toxoplasmosis** which is ongoing. A PET CT is performed which finds increased hilar lymph node avidity prompting bronchoscopy and EBUS. Biopsy of the hilar lymph nodes show sinus histiocytosis without any granulomatous inflammation seen. Metagenomics performed on BAL washings is positive for *Pneumocystis jiroveci.*

## Recent Imaging



**Figures 3 & 4** MRI Head Images, March 2026, showing new cerebellar lesions, improvement in known lesions

## Discussion – The Road Ahead

Central nervous system histoplasmosis is a rare diagnosis encountered primarily in patients with advanced immunosuppression (1). This parasitic dimorphic fungal infection is acquired through inhalation of fungal microconidia which convert from a mold to a yeast form inside macrophages. Usually confined to the lungs, immunosuppression is a risk factor for disseminated histoplasmosis. In this patient's lamentable case, **African Histoplasmosis** (spp *Histoplasma capsulatum* var. *duboisii*) is suspected due to his place of origin. The new CNS lesions have raised concern for a second intracranial pathology and empiric treatment for cerebral toxoplasmosis was commenced in April 2026 with repeat contrast-enhanced MRI head planned to assess evolution of the lesions.

A compassionate access application has been submitted for **Olorofim (2), a first in class oral orotomide antifungal agent** as an alternative to azoles due to poor drug levels which may be explained by ultra-rapid metabolism via CYP2C19 enzymes (3). Significant concern remains around this patient's poor recovery after seven months of treatment. This young man remains **bedbound with advanced sarcopaenia**. He has a dense abulic phenotype likely related to his frontal CNS disease and engagement with therapists is poor. While his weight is slowly up-trending with supplemental NG tube feeding, he remains under 50kg. His HIV viral load is undetectable in serum and CSF and his CD4 count is 39 cells/mm$^3$.

## References

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2. Maertens, J. A. *et al.* Olorofim for the treatment of invasive fungal diseases in patients with few or no therapeutic options: a single-arm, open-label, phase 2b study. *The Lancet Infectious Diseases* **25**, 1177–1188 (2025).

3. Dean, L. Voriconazole Therapy and CYP2C19 Genotype. *Medical Genetics Summaries [Internet]* https://www.ncbi.nlm.nih.gov/books/NBK552035/#:~:text=Interindividual%20drug%20serum%20concentrations%20vary,)%20(4%2C%205). (2019).