CNS lesion – Looking for a solution in HIV patient

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CNS lesion - Looking for a solution in HIV patient

History

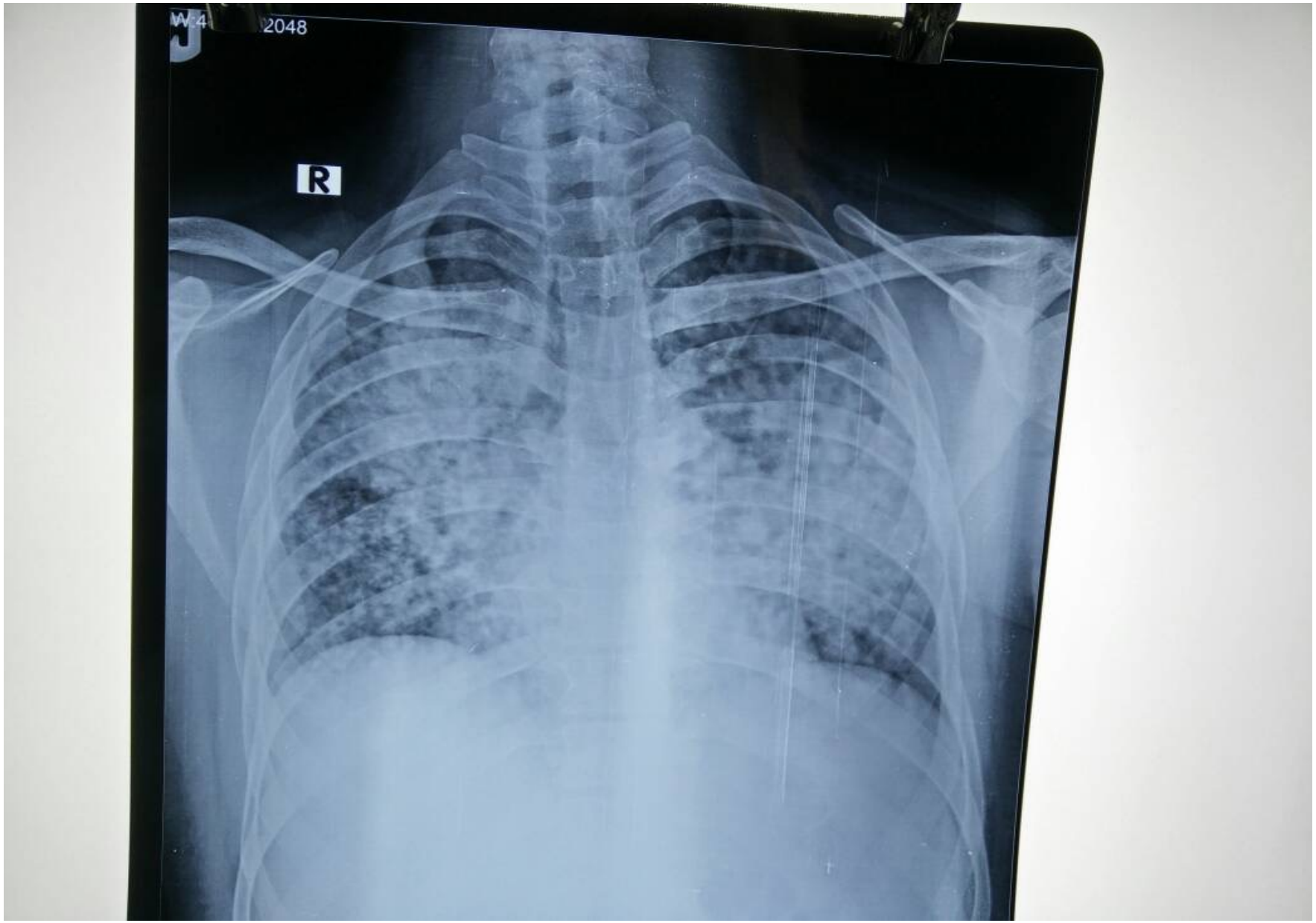
- A 30 year male from Viramgam, Gujarat presented on 27/4/17 with
  - Fever, low-grade evening rise
  - loss of appetite, generalized weakness
  - Coughing(Dry), weight loss 5 kg in 2 months - since 20 days.

  Consulted physician
- **Blood Ix** : Hb:15.7, TC:10500, DC: 75,22,1,2, PC:1.93,P/S: -ve, ESR:43mm

- **X ray chest** : Patchy soft tissue opacity noted in bilateral mid lower zone perihilar region with multiple small nodular opacity noted in right upper mid lower zone & left upper mid lower zone.

S/O **bilateral pulmonary consolidation with nodular infiltration- Koch's etiology.**

X RAY CHEST(P/A) 27/4/17



After 1week Consulted pulmonologist

Investigation :

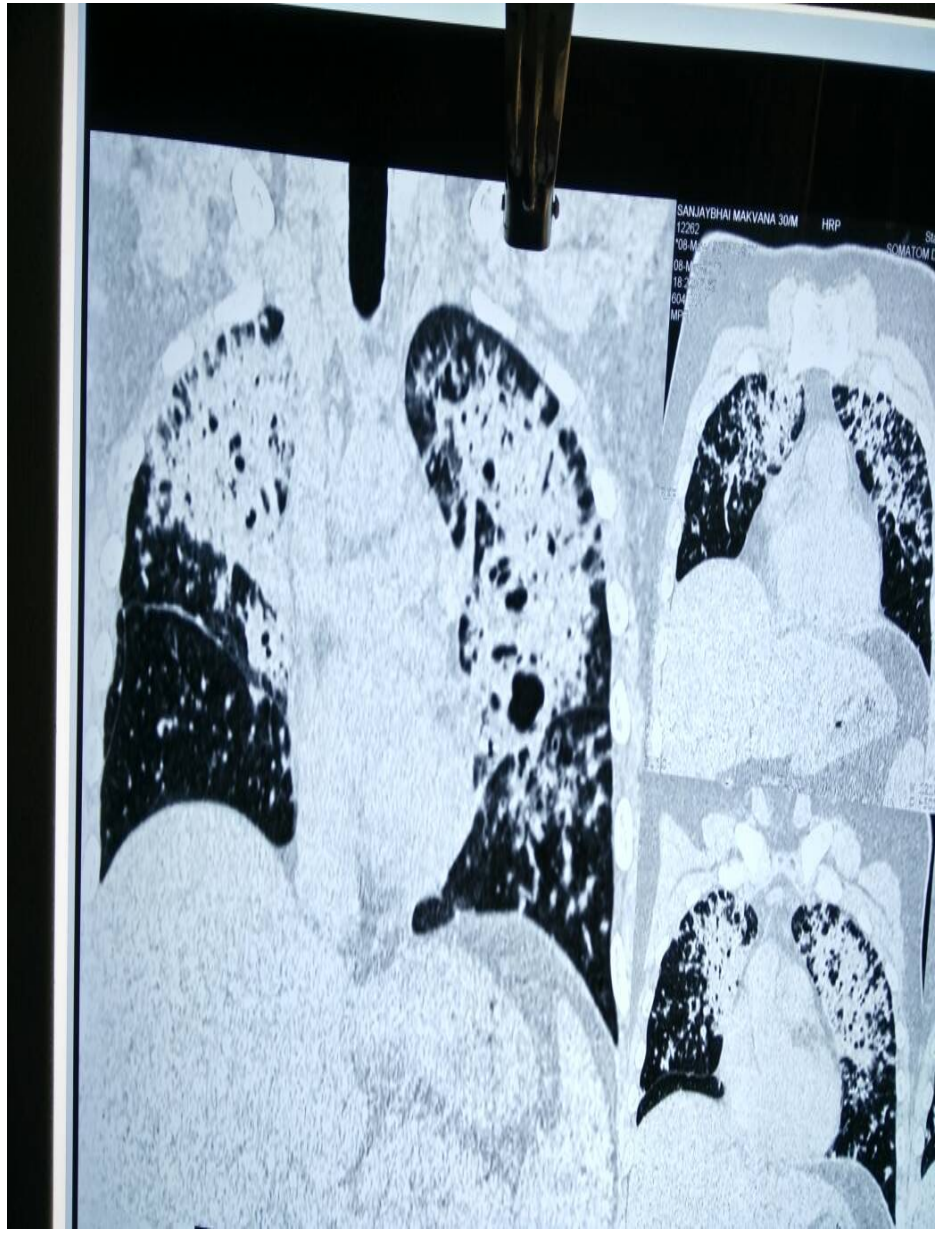
RBS :97. SGPT: 30.4, BIL: T: 0.53, D:0.11, I :0.42**. HIV-1: Reactive**

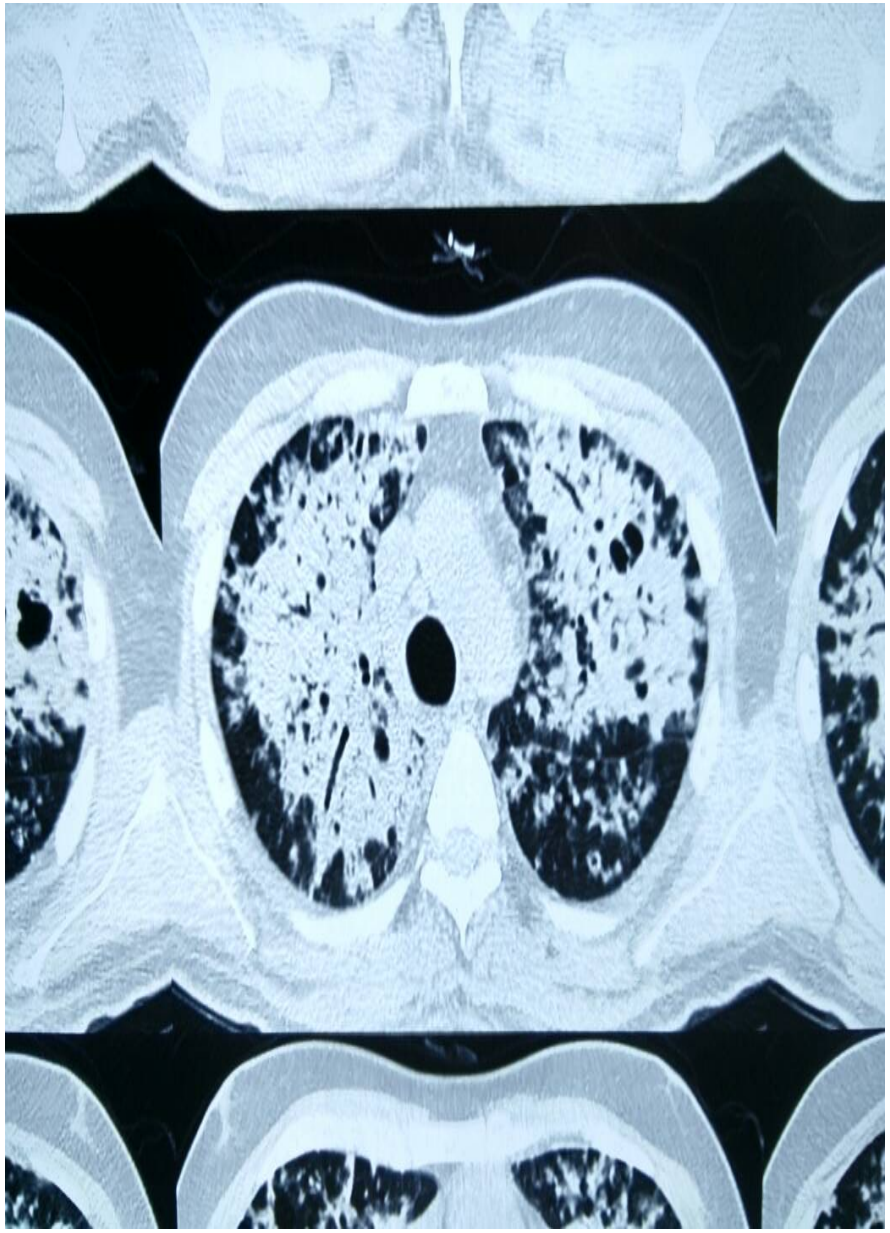
HRCT thorax : Significant area of parabronchial air space consolidation with cavitary areas are seen involving bilateral upper lobes & perihilar region along with multiple other discrete nodular opacities in bilateral lower lobes right middle lobes as well as lingula. Few other nodular cavitary lesions involving bilateral lower lobes. Multiple mildly enlarged pre & paratracheal, perivascular & subcarinal groups of mediastinal lymph nodes.

S/O : Infective bronchioalveolitis probably Koch's with secondary infection fungal likely.

Empirically AKT with Supportive management but still no relief

HRCT THORAX (8/5/17)





On 13/5/17 Consulted ID Specialist

On presentation

- Fever, low grade evening rise,
- Dry coughing – 1month
- NO GI/GU/CNS/ complaints

Physical Examination

- Vitals – T-99.8F. P-84/min, BP-124/84mmHg, RR-16/min. Spo2-98 on room
- No Anemia, No Icterus, No palpable lymph nodes, No skin lesions
- R/S- Bil crepitation, CVS,P/A,CNS : NAD

Investigation

- HB:14, TC:8400, DC: 67/26/1/6/0, PC:2.21
- SGPT: 32, Bilirubin:1.1,
- Creatinine: 0.89mg%, sodium-138, potassium-4.2.
- TPHA, VDRL : -ve, Toxoplasma- IGG:0.40 ,
- HBsAg : -ve, HCV : -ve,
- **CD4 count: 72 cells/cmm**
- S. Cryptococcal antigen : -ve.
- **USG abdomen & bilateral neck & axilla** :

- Solitary enlarged (1.3cm) node in right lower neck. few enlarged (1.7 cm) nodes in superior mediastinum. mild splenomegaly.

- Differential Diagnosis ?

Differential diagnosis

- Tuberculosis
- PCP
- Invasive Mold Infection
- Atypical Bacterial Infection
- Viral Infection(CMV, Hanta virus)
- Pulmonary Haemorrhage
- Interstitial lung diseases
- Other cause(NTM, Histoplasma, Nocardia, Lymphoma)

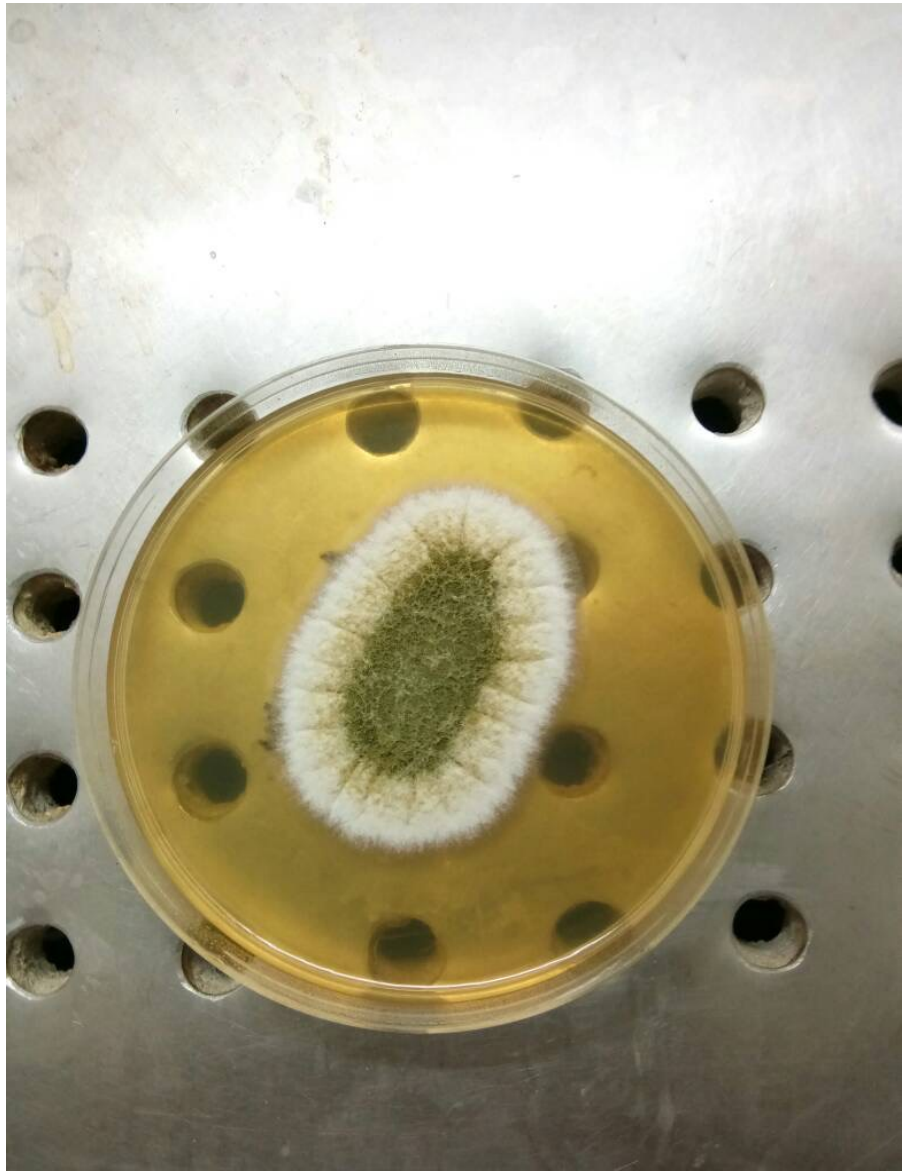
- Further Investigation?

Investigations

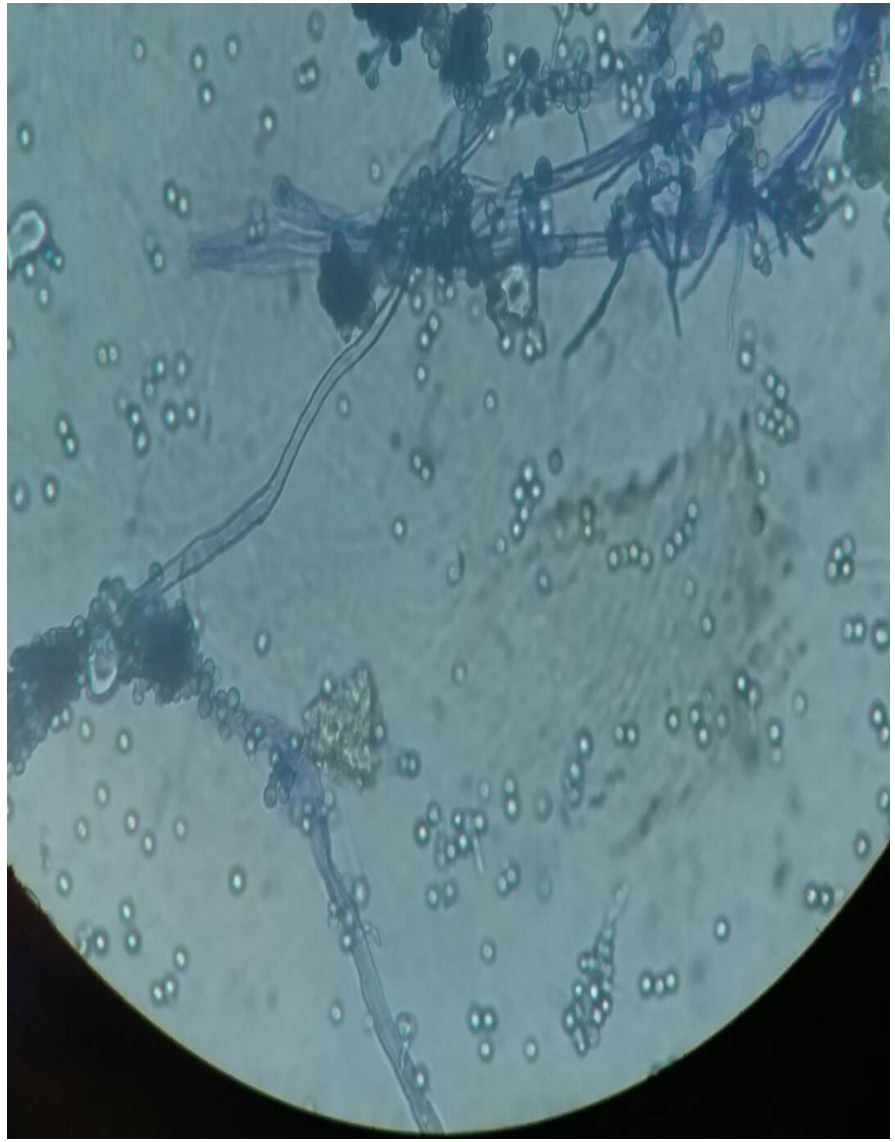
On 15/5/17 Bronchoscopy & BAL

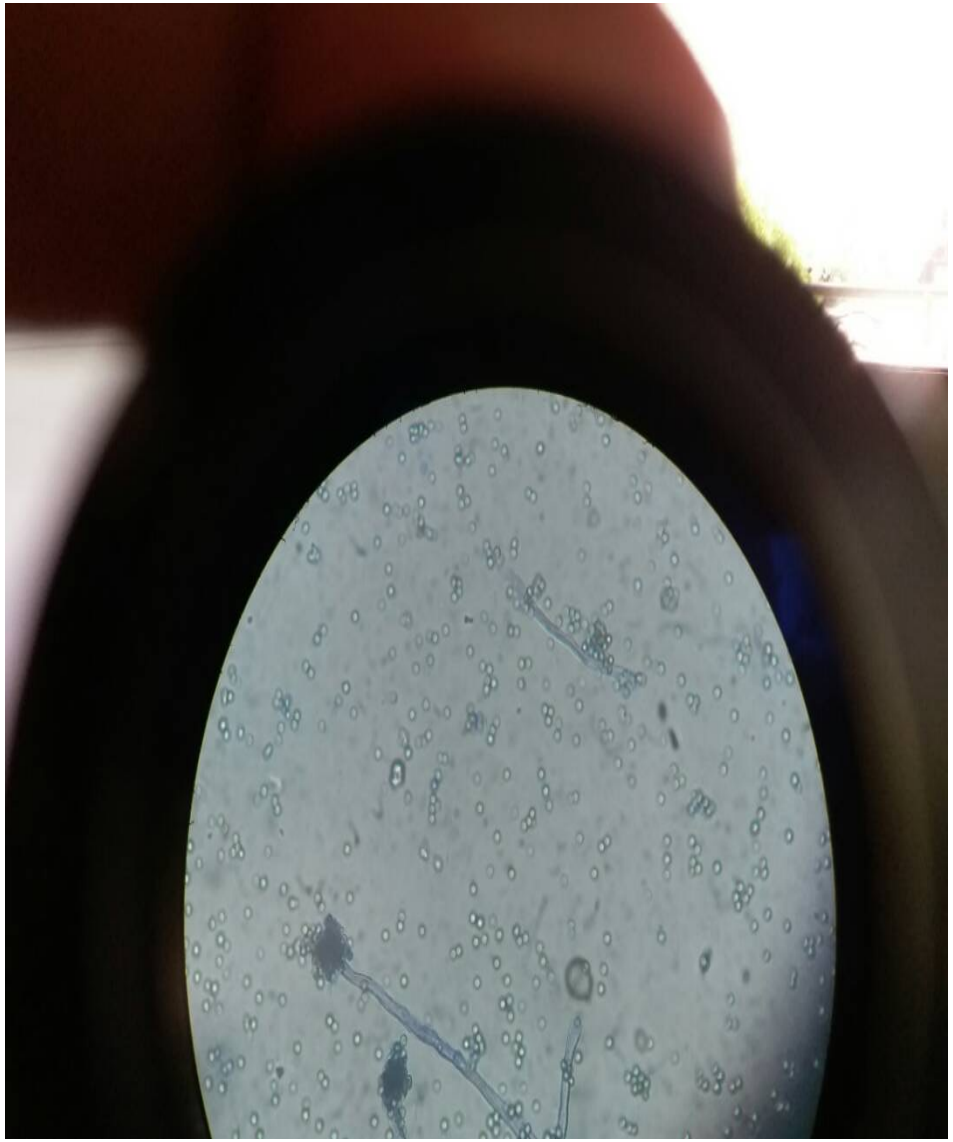
- BAL for galactomannan 0.28 (-ve),
- No cysts of Pneumocystis jiroveci seen
- Gene x pert MTB/RIF : MTB not detected
- KOH preparation: **Septate branching hyphae**
- Pyogenic c/s: Negative
- Fungal c/s : **Aspergillus flavus** isolated
- AFB c/s : No growth

- Tissue HPE : Lung tissue with focal infiltrates of lymphocytes and foamy histiocytes and focally frothy material



Microscopic Image Aspergillus flavus





BAL Galactonannan –ve and Fungal C/S Aspergillus flavus +ve

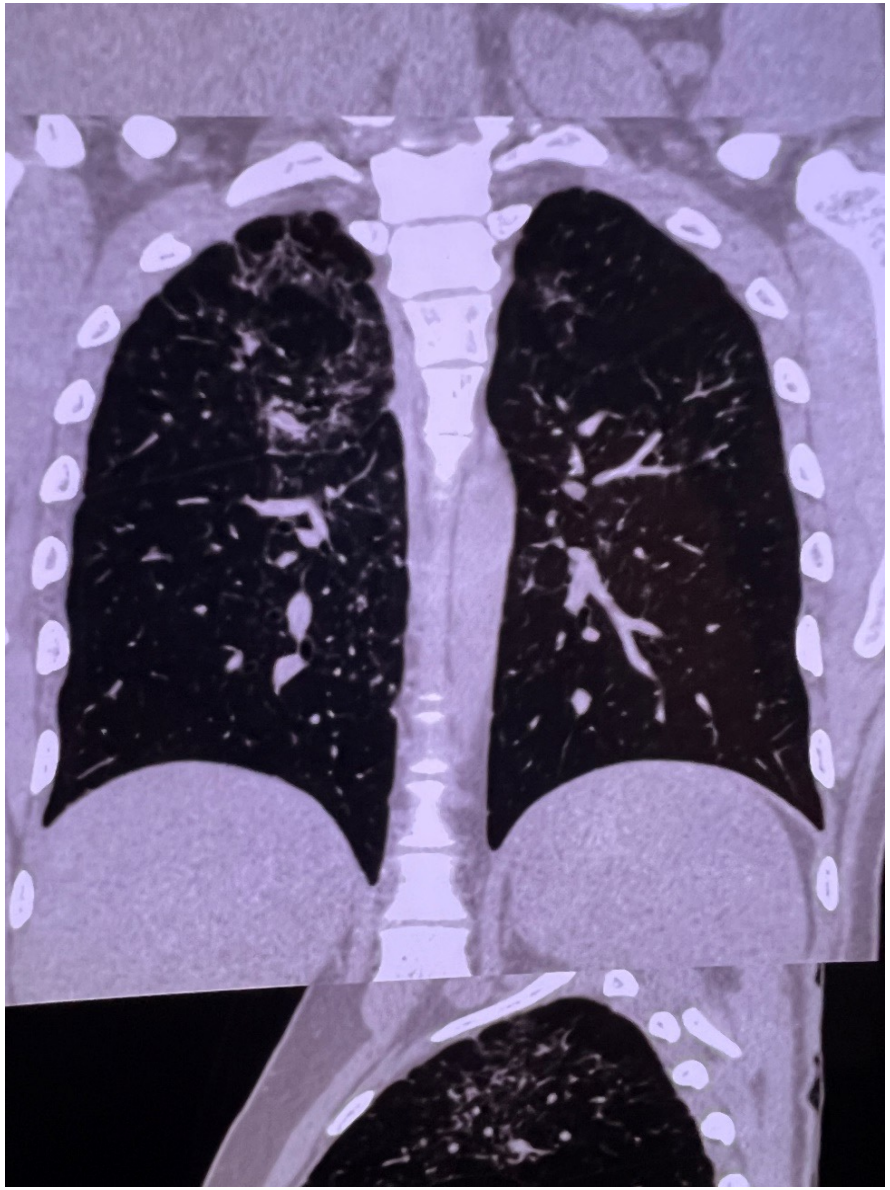
Significance?

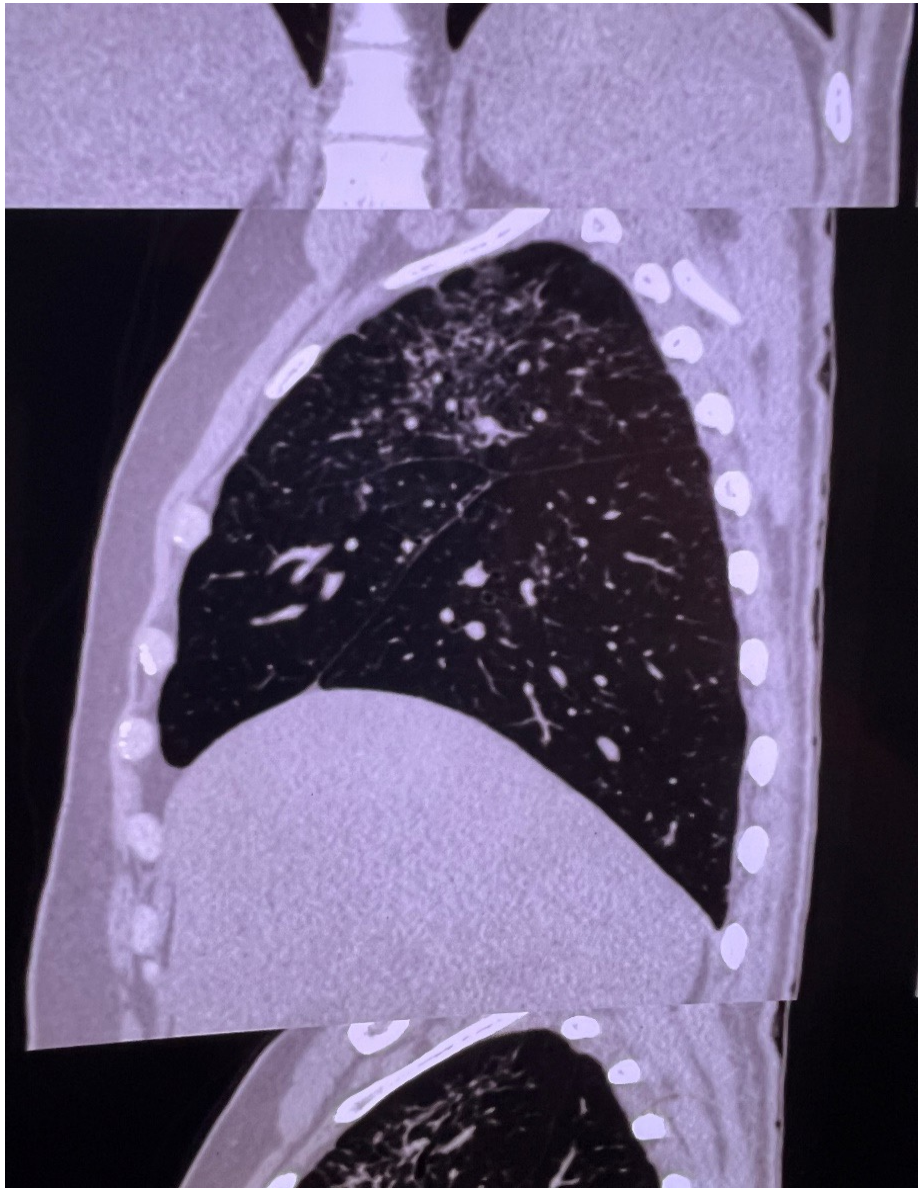
Treatment

- Voriconazole
- TMP-SMX
- Voriconazole trough level : 1.28(1-5.5)
- LFT,RFT – normal
- ARV(TDF+FTC+NVP[ER]) – after 45 days
- After 3 months
  - X-ray chest(PA): normal,
  - HRCT Thorax – improved,
  - Absolute **CD4 : 278** cells/cmm

- Voriconazole and Nevirapine

9/9/17 HRCT Thorax





Follow up

- Incomplete adherence
- Unscheduled visit for OPD every time
- ARV(TDF+FTC+NVP[ER])
- TMP-SMX
- CBC, LFT, Creatinine, Electrolytes every time within normal limit

CONSECUTIVE CD4 STUDY

DATE	13/5/17	16/11/17	14/6/18	25/1/19	16/11/19	6/2/21
ABSOLUTE CD4 COUNT	72	278	164	163	178	110
CD4 %	3%	6%	6%	5%	6%	4%
ABSOLUTE CD8 COUNT	1920	4028	2265	2762	2497	2391
CD8%	80%	87%	83%	85%	84%	87
CD4/CD8 RATIO	0.038	0.069	0.072	0.059	0.071	0.046

Recurrent ART Defaulter

On 10/3/2021

- SJ Syndrome(? TMP-SMX,? NVP) and Viral Diarrhea
- Viral Load – 565000 copies/ml
- HLAB5701 : -ve
- Treatment changed – ABC+3TC+DTG, Dapsone
- Maintaining good CD4 for 1 year

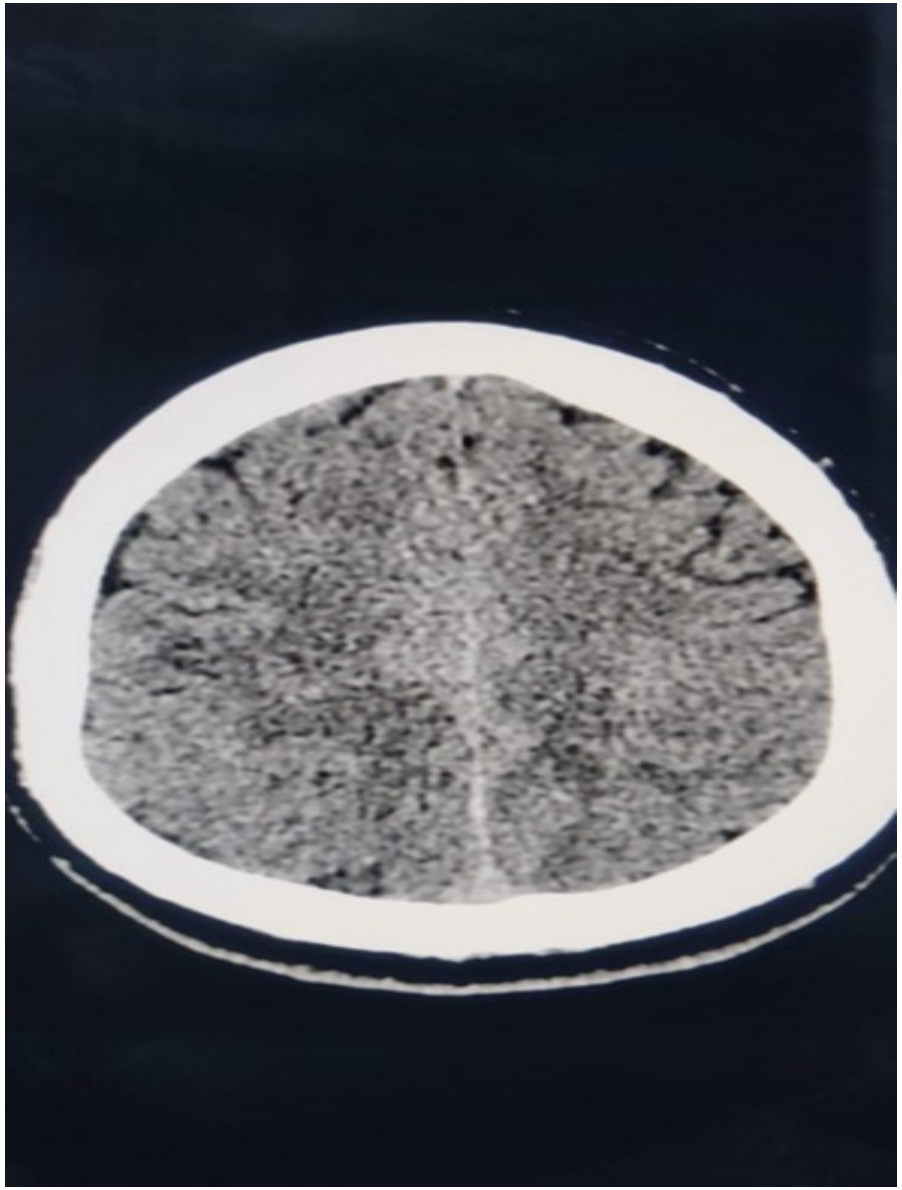
CONSECUTIVE CD4 STUDY

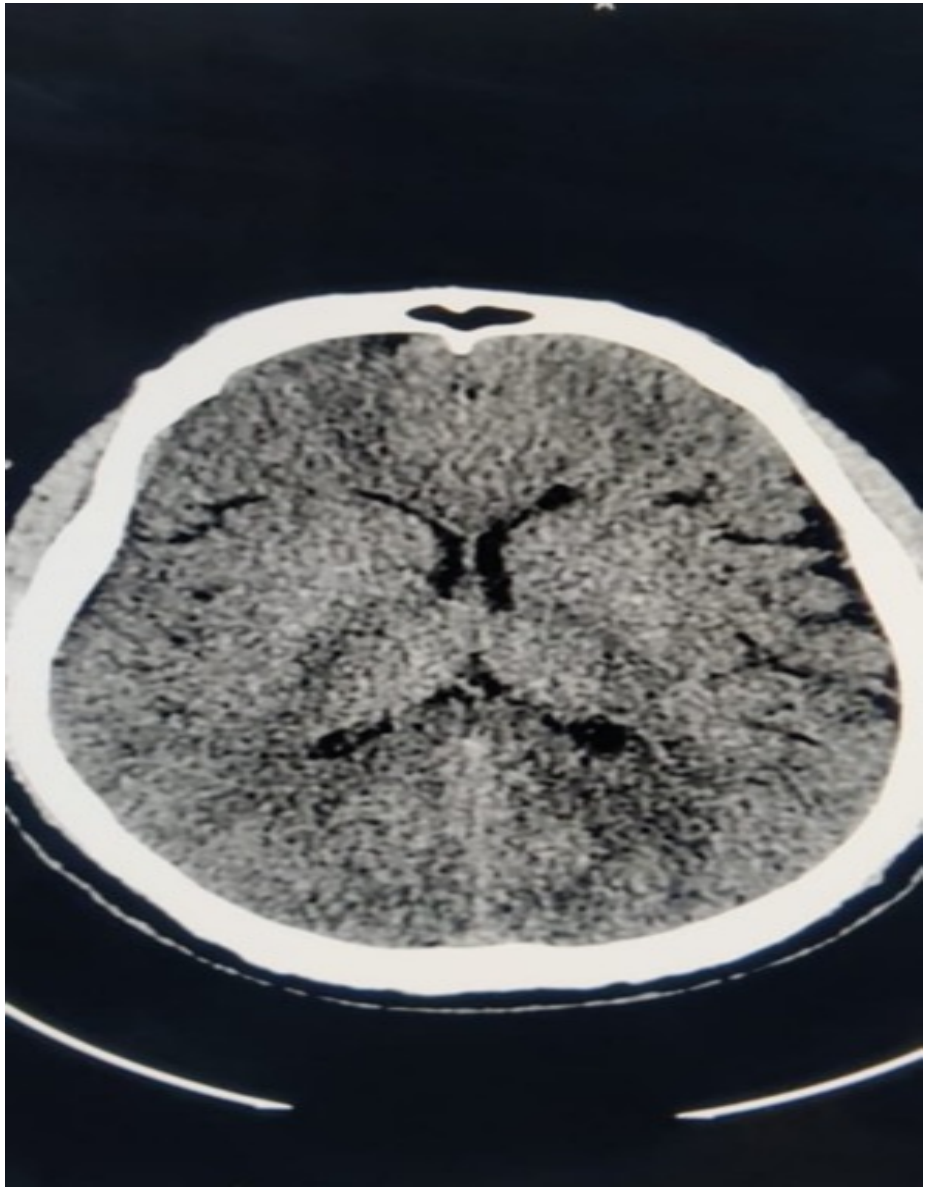
DATE	10/7/21	23/10/21	12/7/22	28/1/23	19/5/23
ABSOLUTE CD4 COUNT	322	365	616	626	552
CD4 %	10%	13%	13%	16%	16%
ABSOLUTE CD8 COUNT	2541	2106	3459	2620	2209
CD8%	79%	75%	73%	67%	64%
CD4/CD8 RATIO	0.127	0.173	0.178	0.239	0.250

On 1/1/22

- Headache(left throbbing)
- CT Brain : Multifocal bilateral **asymmetrical**(L>R) periventricular and subcortical hypodensity involving bilateral fronto-parieto-occipital lobes – **PML**
- Not willing for MRI, CSF
- Steroid started(methylprednisolone followed by prednisolone) – 3month used
- Asymptomatic within 10 days of steroid
- ART continue same – ABC+3TC+DTG from 1/1/22 to 11/6/23

CT Brain – 1/1/22

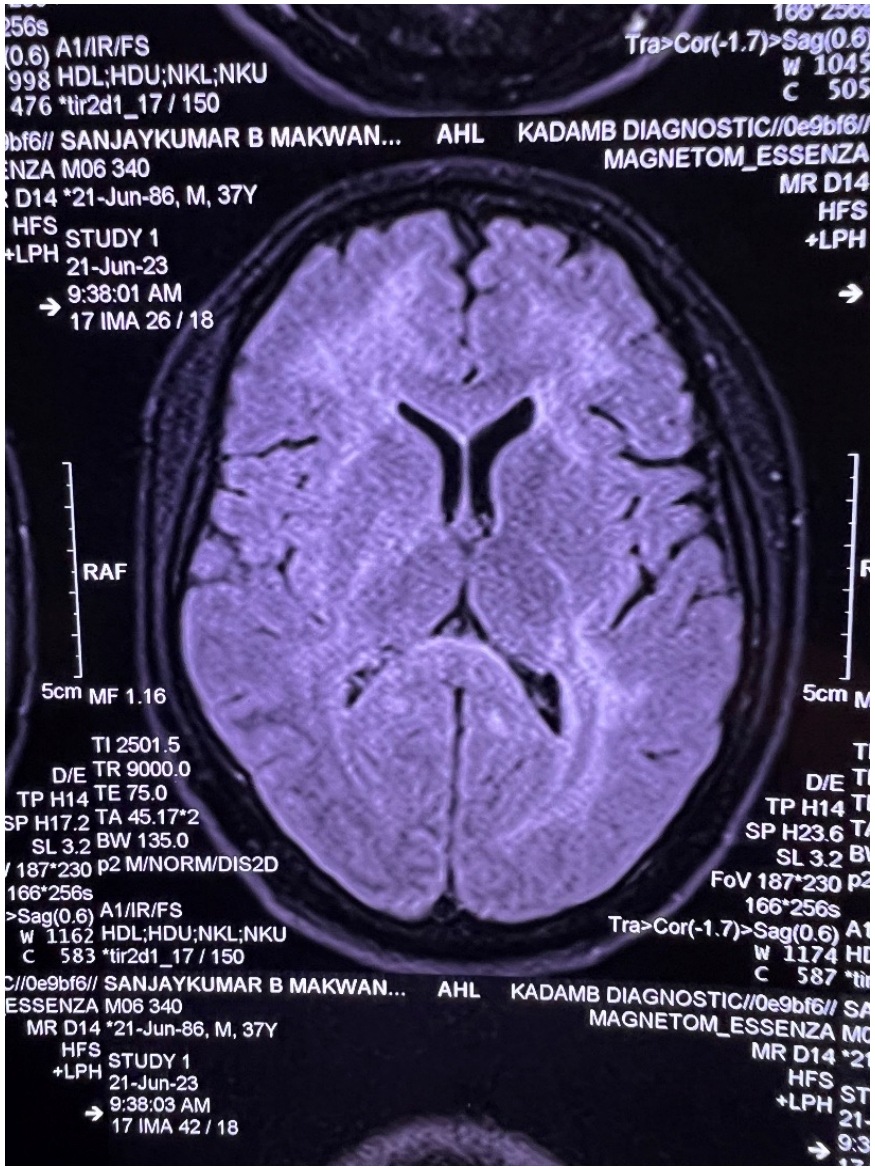


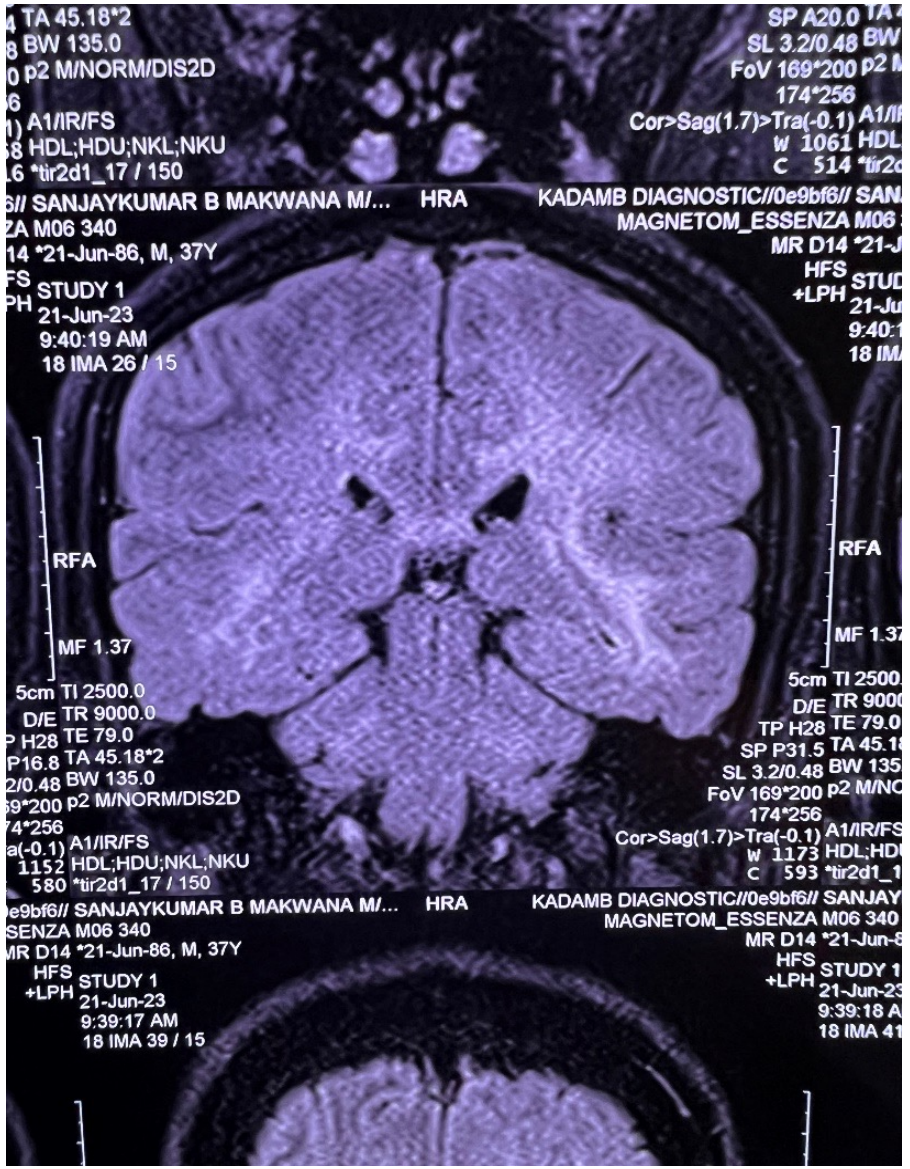


On 20/6/23(after 18month)

- Giddiness, **GTCS** and Fall down
- **MRI Brain** – Diffuse almost **symmetrical** areas of T2W and FLAIR hyperintensity involving bilateral fronto - parieto-temporal white matter involving deep and peripheral white matter extending along internal capsule along with involvement of corpus callosum, Patchy hyperintense areas in brainstem and cerebelli - **PML**
- **CSF Examination** : TC-30, Lymphocytes -100%,Gene X-pert – MTB not detected, JC virus DNA PCR – Not detected
- CBC,RFT,LFT, Electrolytes – Normal
- **Plasma Viral load – undetected, CD4- 552**.
- Steroid(2months), levetiracetam, ART same continue

MRI Brain (21/6/23)





After 9 Month

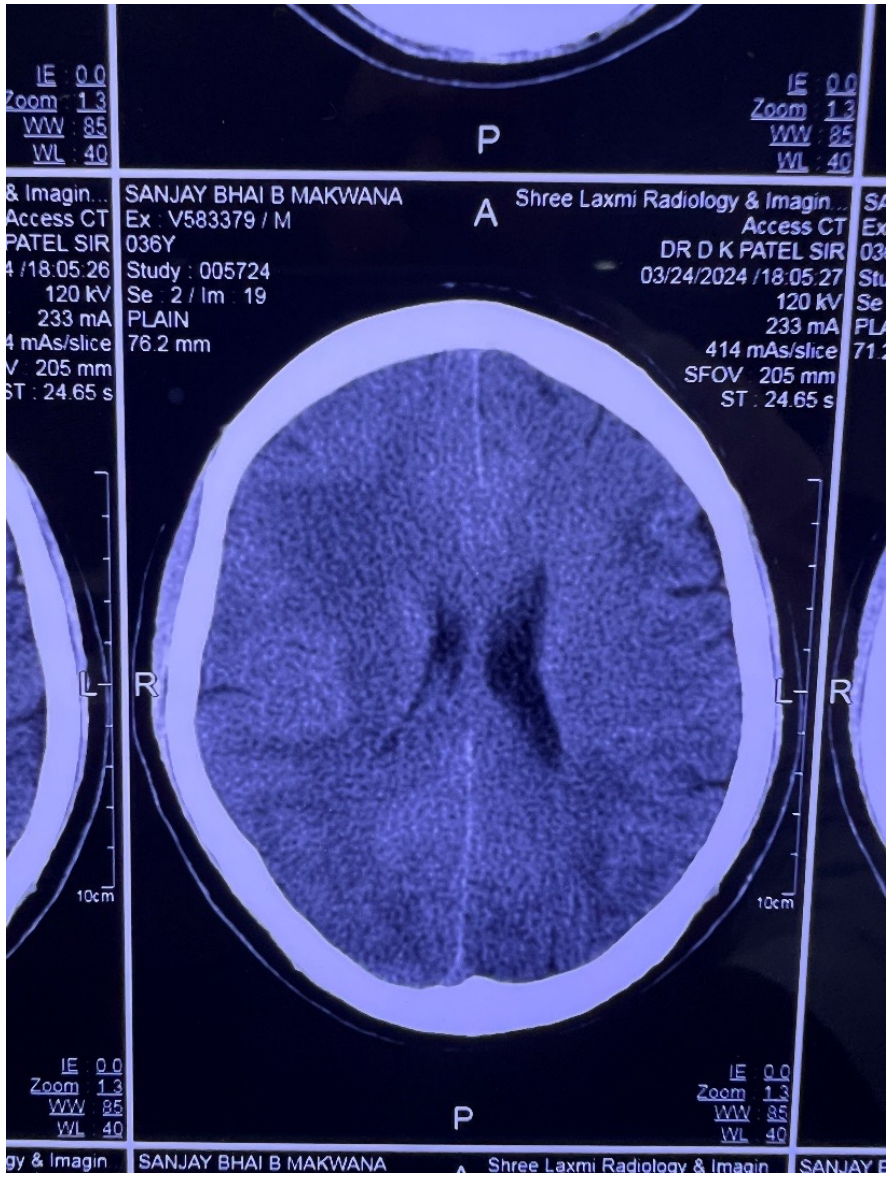
On 25/3/24

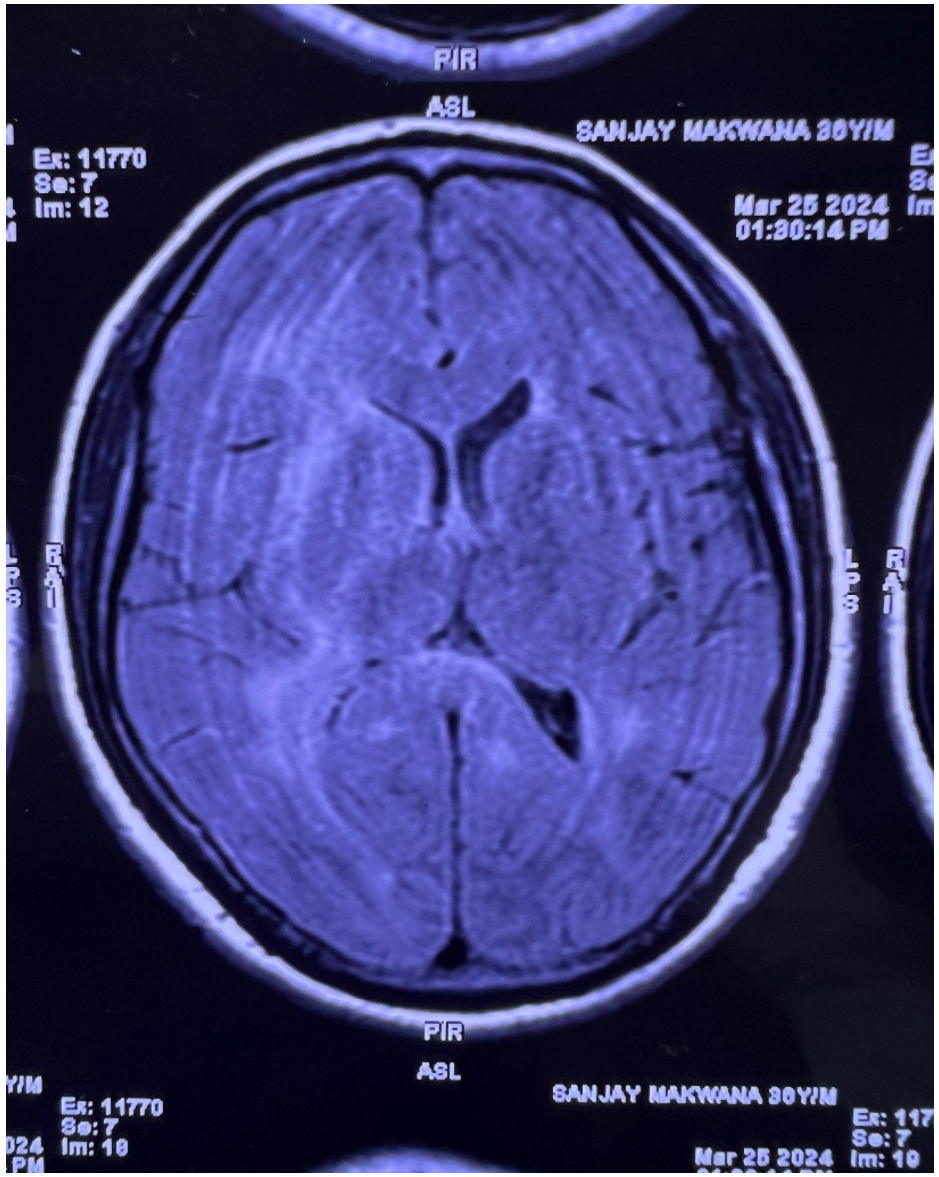
- Headache, Vomiting, Drowsy, **Right UL & LL weakness**
- Consulted Neurologist
- **MRI Brain** + **Angiography** – Large **asymmetrical** periventricular white matter lesion as previous site but **increases lesion** - **PML**

 - Angiography-normal

- CD4-544
- Treatment- Steroid responsive - maintenance dose- omnacortil -5mg daily ongoing

MRI brain(25/3/24)



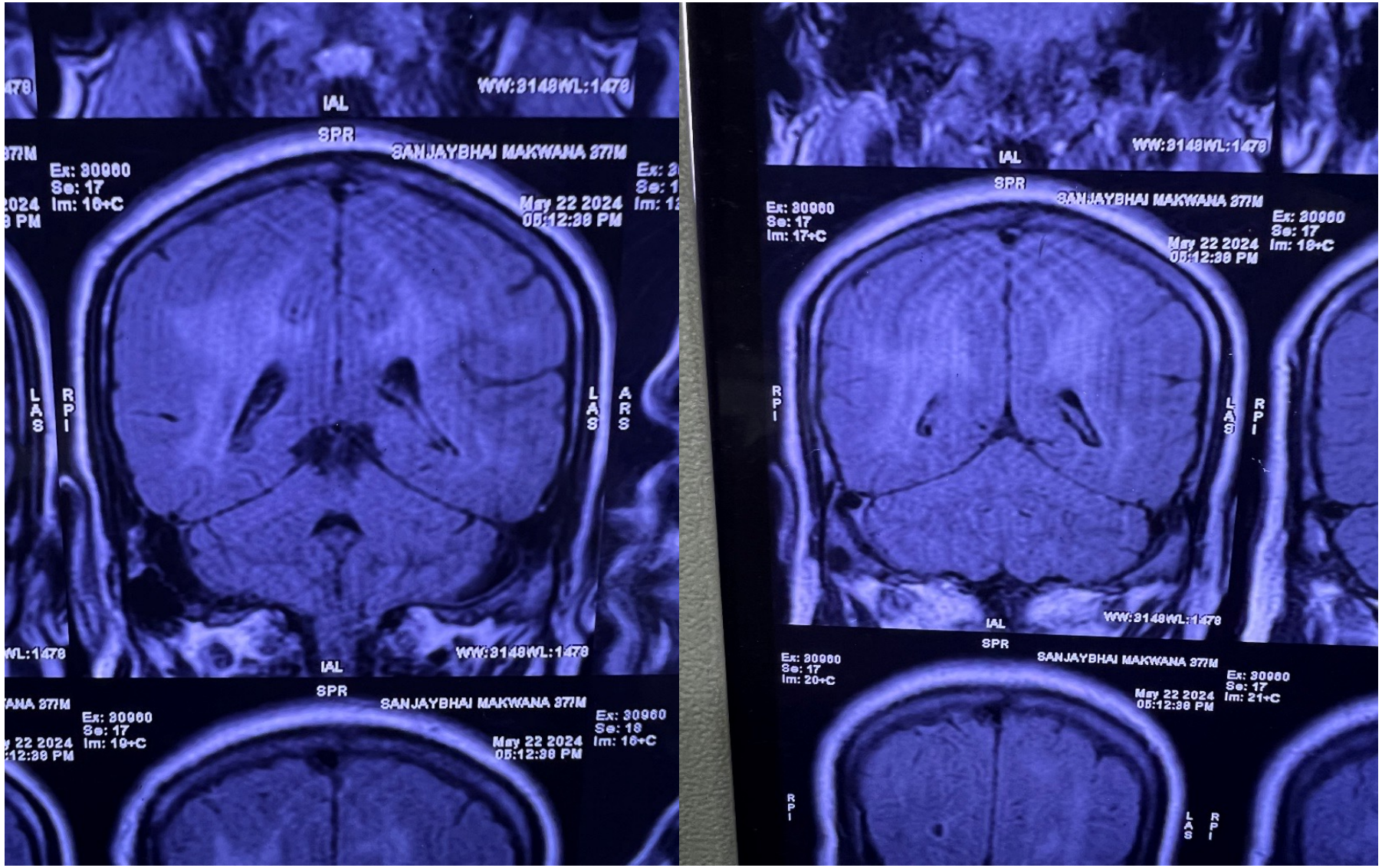


After 2 months of last episode

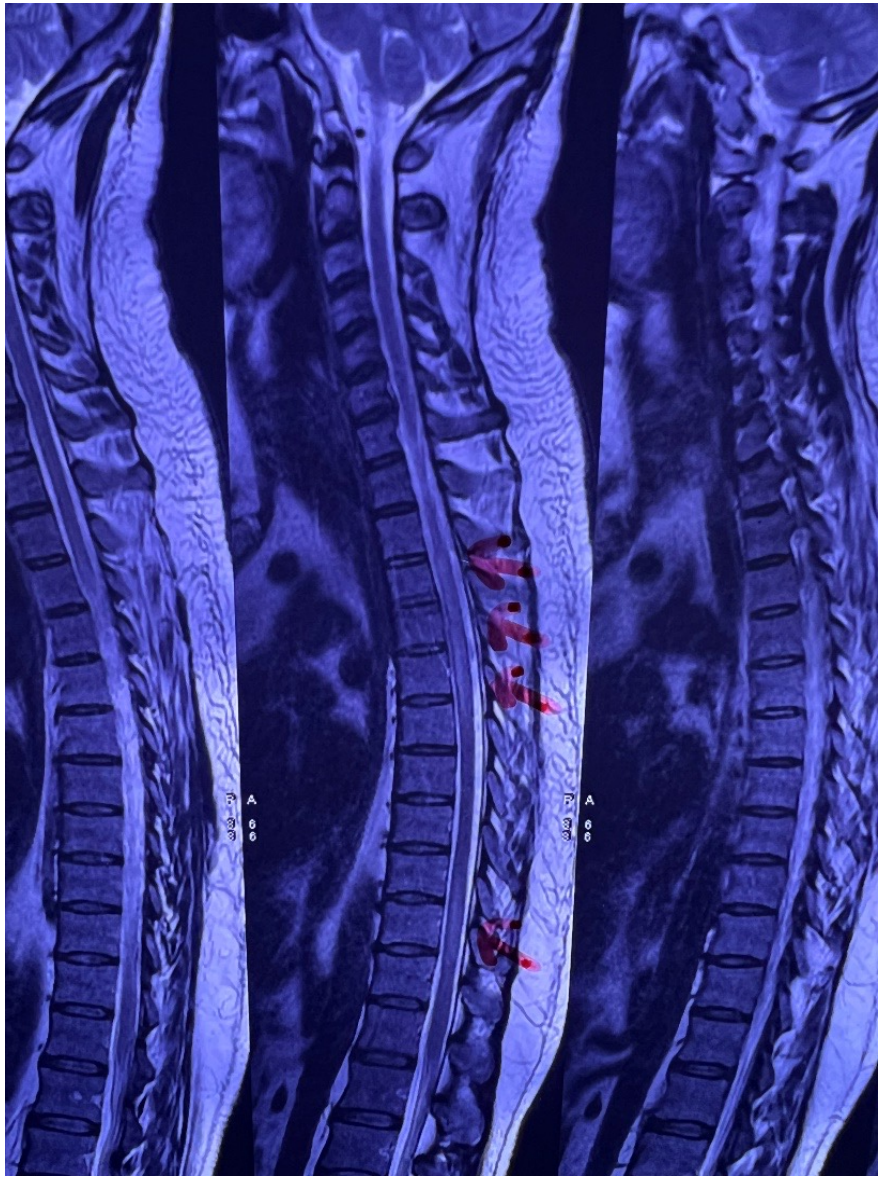
- Ongoing 5mg omnacortil
- **Lower backache,** imbalance while walking, hypersomnolence, **visual disturbance**
- Consulted Neurologist
- Examination- conscious, oriented, gait ataxia
- **MRI Brain** + **Whole spine screening-** Large confluent **asymmetrical** T2W/FLAIR hyperintense areas involving deep white matter and subcortical U-fiber of bilateral fronto-parieto-temporo-occipital lobe, left caudate nucleus, left internal capsule and bilateral cerebral peduncle – **PML**, resolving lesion in pons and cerebellum

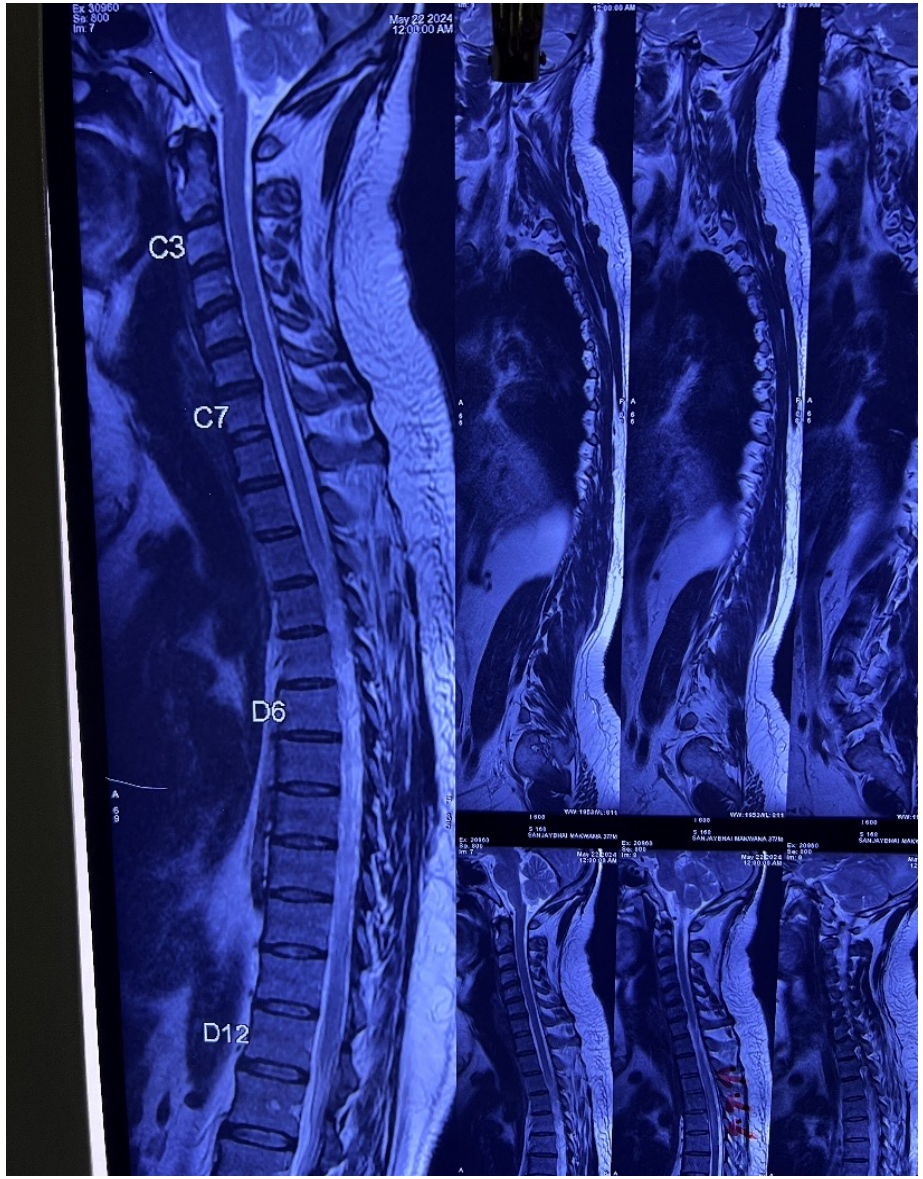
Spine – Abnormal T2 hyperintense signal involving dorsal spine from D3 to D6 level & D9 to D11 level – **Demyelinating lesions(of PML likely)**

MRI brain (22/5/24)



MRI spine (22/5/24)





- **CSF examination** : TC-80, poly-05, lym-95, RBC-30, protein-83(15-40), glucose-113(50-80), Matching sugar – 124
  - AFB-Not detected,
  - JC Virus DNA PCR- Not detected,
  - TPHA–ve,
  - India ink –ve for cryptococcus, CRAG: -ve,
  - Biofire –ve,
  - Electrophoresis - +ve for oligoclonal bands,
  - NMO-MOG Antibody –ve
- **CSF Viral load – 2008 copies/ml**
- **Plasma Viral load – 218 copies/ml**
- Serum ANA –ve, C-ANCA,P-ANCA –ve.

Differential diagnosis?

Differential diagnosis

- Retroviral illness with Viral Escape
- Retroviral with PML in brain and demyelinating lesion in spine
- Retroviral with demyelinating disorder(NMOSD) in spine
- HIV-associated Encephalopathy
- HIV-associated Myelopathy
- HIV-associated Neurocognitive Dysfunction(HAND)
- Any other cause

- In view of presence of confluent T2W/FLAIR hyperintensity,(initially asymmetric and now predominantly symmetric), and Spinal cord involvement is highly **unusual for PML.**

- Though the confluent bilateral cerebral white matter involvement is similar to seen in **HIV associated encephalopathy**, however posterior fossa involvement is unusual.
- Similar long segmental spinal cord as well as bilateral cerebral hemispheric involvement can be seen in **HIV associated myelopathy**.

(However, both these conditions are associated with significant immunosuppression and reduced CD4 count)

HIV with Viral Escape possible

Treatment

- Steroid – Pulse therapy- 1gm methyl prednisolone for 5 days,
- MMF – 500mg BD
- Gradually steroid tapered upto 5mg/day (omnacortil) and MMF increased-1000mg BD
- ART same continue – ABC + 3TC + DTG

After 4 months of last presentation

On 4/10/24

- Headache, **Visual disturbances**, Imbalance and Tingling in both LL
- **MRI brain/Orbit/Spine** – Multiple confluent & discrete non enhancing T2W/FLAIR hyperintensities without diffusion restriction involving periventricular and deep white matter of bilateral cerebral hemispheres, genu and body of corpus callosum, subcortical white matter of bilateral insula, left capsuloganglionic region, left thalamus, left cerebral peduncle with focal involvement of subcortical white matter in bilateral frontal and right anterior temporal lobes.

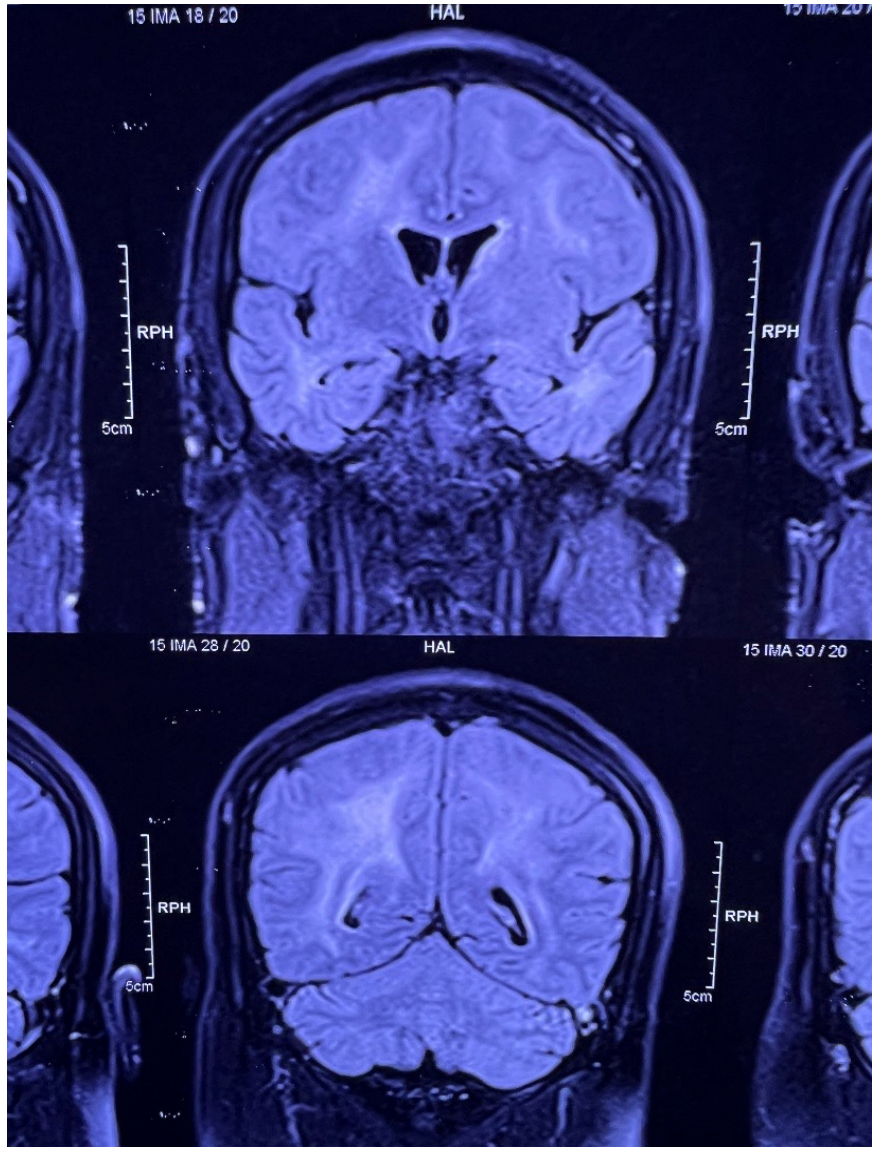
  Orbit – normal

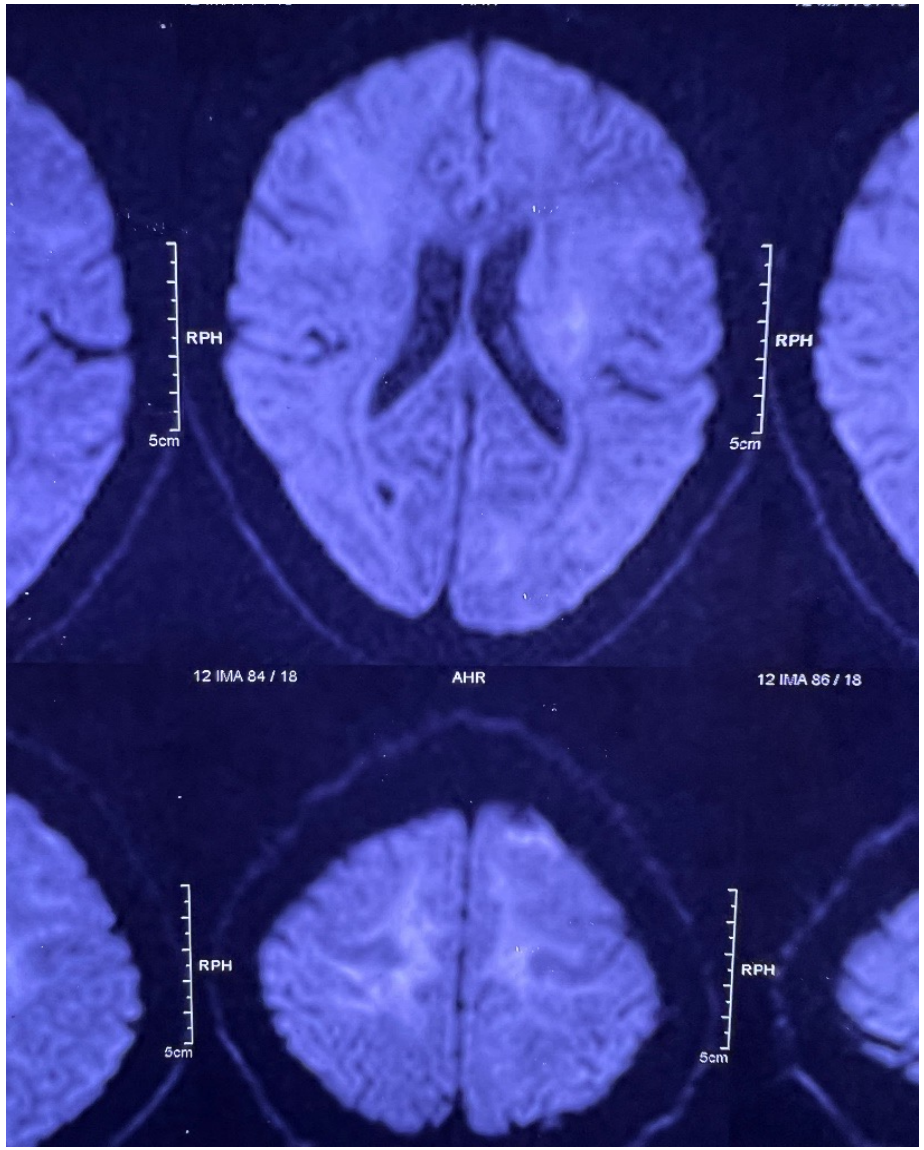
  Spine – only posterior bulging of L4-L5 and L5-S1.

CSF – TC-28, poly-05,lym-95, protein-47,glucose-146

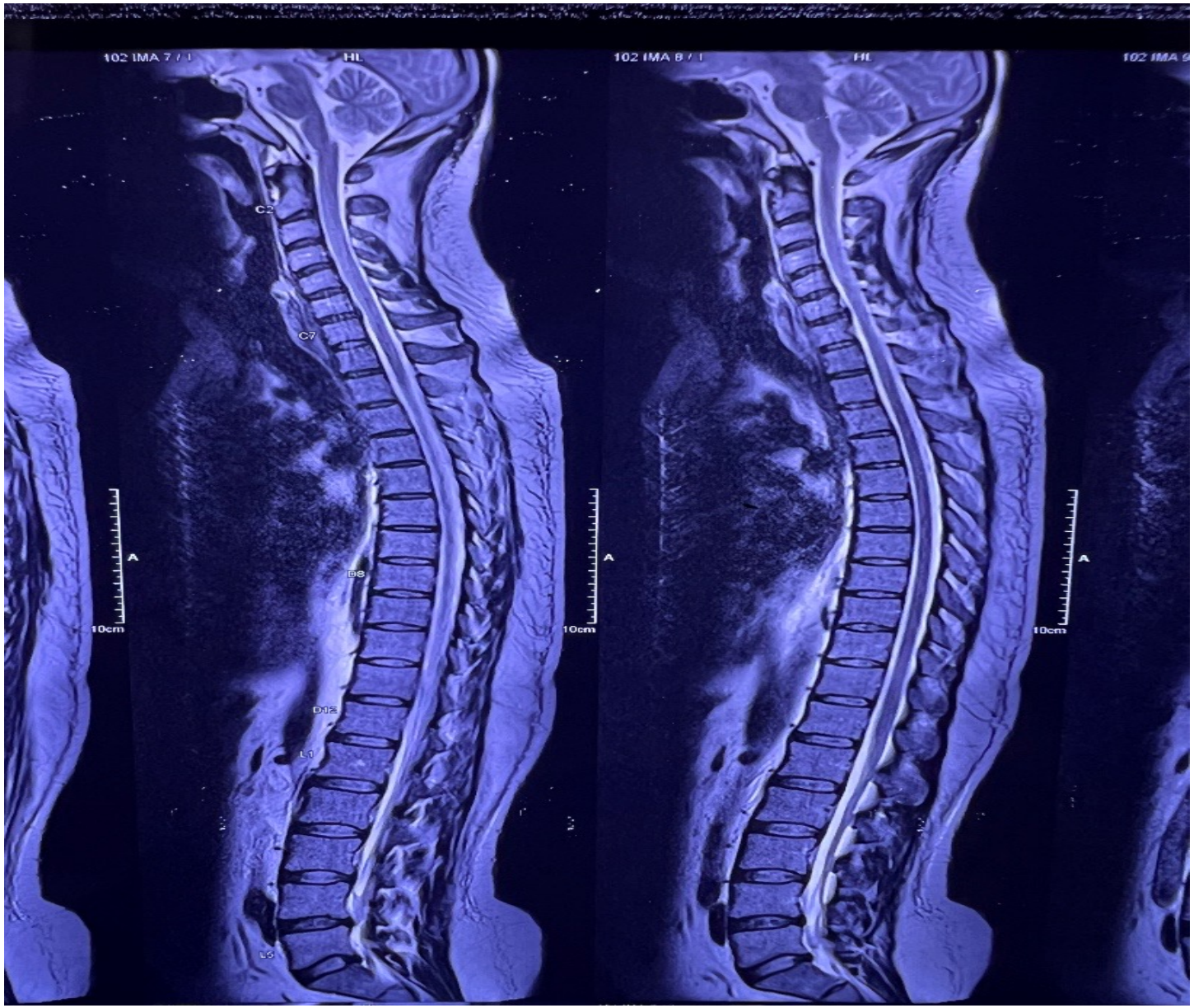
Treatment – Pulse therapy steroid and oral MMF continue

MRI Brain(5/10/24)





MRI spine (5/10/24)



ID consultant opinion

- **Plasma Viral load – 695 copies/ml**
- **Serum CD4-367**, %-17.1, CD8-1292,%-60.2, CD4/CD8 ratio-0.28.

- **CSF Viral load – 4010 copies/ml**

CSF – TC-200,Poly-10,Lym-90,Protein-82,Glucose-82.

- CSF CD4/CD8 study- **CD4-13**, %-7, **CD8-160**, %-89, CD4/CD8 ratio-0.079. **CD8/CD4- 12:1**.

- **HIV Resistance testing** both from Serum and CSF – Not possible because of low detectable Viral load

Final Diagnosis ?

Radiological Features

- Imaging differential consideration of **HIV associated CD 8+ encephalitis** can be considered in view of increase in the confluent supratentorial – infratentorial involvement in March 2024 showing response to corticosteroids. Spinal cord involvement though rare is also reported in CD 8+ encephalitis

Final diagnosis – Relapsing CD8+Encephalitis

- Treatment :

  1) ART Changed – 3TC + DTG + DRV/r

  2) Steroid – Pulse therapy methylprednisolone then tapered omnacortil upto 5mg,

  3) MMF- 500mg 1BD

Relapsing CD8+ encephalitis

- CD8+ encephalitis (CD8+E) is an emerging and **incompletely understood HIV associated neurological syndrome**, typically presenting as a steroid – responsive subacute encephalopathy with prominent white matter changes in patients with apparently well – controlled HIV infection.

- Some cases can be associated with the phenomena of 'viral escape' (disproportionate replication within the cerebrospinal fluid), but the **most important pathophysiology** of CD8+E is thought to involve an attack of HIV – infected CD4+ lymphocytes by autoreactive CD8+ cells.

- Although a **definite diagnosis** of this syndrome is only possible **histologically,** and is often only made at autopsy, the clinical picture in this case was considered convincing enough to avoid the significant risks of brain biopsy, and empirical treatment for CD8+E was considered appropriate.

- 4 main triggers for CD8+E :
  - Viral escape,
  - Immune reconstitution syndrome (IRIS),
  - Another viral infection,
  - An interruption of cART therapy.

- **Viral escape** as the main driver of the CD8+E should be considered early on in the disease course and even when there is no initial resistance noted, repeated viral resistance testing needs to be implemented as the early change of cART may help in the long term management of CD8+E and achieve better viral suppression in the CNS and prevent further relapses.

- Classical presenting features of CD8+E include **headache, worsening confusion and seizures.** Our patient exhibited most of the features during her numerous admissions, though **ataxia seem to be much rarer clinical presentations of the syndrome**

- CD8+E has similarities with the well – recognized **'diffuse infiltrative lymphocytosis syndrome'** where CD8+ lymphocytes infiltrate the salivary glands, lungs and sometimes peripheral nerves.

- Radiological hallmarks of CD8+ include diffuse high – intensity white matter signal and multiple punctate or linear lesions. **Our patient demonstrated relapsing – remitting diffuse white matter changes** on T_2 MRI and cerebral oedema. Gray et al[7] have shown diffuse CD8+ lymphocyte infiltration into perivascular spaces and within brain parenchyma.

- Although the clinical condition remained exquisitely **steroid – sensitive**, subsequent repeated attempts to reduce the dose of prednisolone below 20mg daily led to a marked worsening of the ataxia, headache and encephalopathy
- Our case of CD8+E where the initial positive response to steroid treatment was followed by several relapses on withdrawal as well as ongoing steroid. This lead to the use of **mycophenolate mofetil (MMF)** as a long – term steroid – sparing agent.
- Developing a steroid - dependent neurological syndrome. There is **no clear guidance on the maintenance dose or recommended duration of steroid therapy,** and no information available on the long term management of patients who cannot be weaned off steroids.
- Untreated CD8+E is often associated with a fatal outcome.

Why **MMF**(Mycophenolate mofetil) choice

- MMF was chosen due to its

  1) Favorable CSF penetration

  2) Relatively benign side effect profile

  3) Absence of significant interaction with cART regimen

  4) Short half - life compared with some alternatives

  5) MMF use in those with HIV and have shown **addictive antiviral benefits**. MMF causes apoptosis of activated CD4+ lymphocytes in vitro with little effect on resting T cells and the lymphocytes of HIV positive patients with uncontrolled viraemia are known to be sensitive to apoptosis.

- Despite treatment with steroids and MMF, our patient had a higher percentage of CD8+ lymphocytes in the CSF in comparison with CD4+ lymphocytes.
- **Plans** are being made to complete the steroid withdrawal, followed by discontinuation of the MMF with ongoing close clinical, radiological and CSF surveillance.

Learning points

- Include cerebrospinal (CSF) flow cytometry and CSF HIV viral load in HIV positive patients with neurological deterioration and diffuse white matter changes on imaging.
- Explore possible triggers of CD8+E : Viral escape, Another viral illness, resistance to interruption of combination antiretroviral therapy (cART), or immune reconstitution.
- Start steroids promptly to prevent mortality/morbidity.
- Look repeatedly for evidence of viral escape or cART resistance
- Further evidence for use of alternative steroid - sparing agents is required.

Thank You