DISSEMINATED GRANULOMATOUS INFECTION

TRACING THE ROOTS…!

Dr Nishant Tomar
DrNB Neurology Resident
BLK-MAX Super Speciality Hospital ,Delhi

Moderator – Dr Rajiv Anand
Dr Varun Rehani

HISTORY

- Mr X , 35 year, male, Paramedic Staff worker at Delhi Government Hospital
- Chief complaints -
  - High-grade fever - 3 day
  - Severe unbearable headache - 2 days
  - Altered sensorium - 1 day
- Recently diagnosed at other hospital as a case of TB

  (clinical + radiology + histology reports) - ATT since 3 wks.
- H/O of wt loss 20 kgs in 3 months.

  (Pre illness wt 70 kgs – admission wt – 50 kgs)
- No H/O TB in past or family

Outside investigations :

- Routine Investigations - Chest Xray - normal
- Ultrasound Abdomen showed ? Right Iliac fossa bowel thickening
- CECT Chest + Abdomen showed multiple conglomerate necrotic lymph node at hilar mediastinal & mesenteric LN.
- **HIV serology & viral markers – Negative**.
- CSF analysis - normal
- EUS guided mediastinal lymph node biopsy showed **granulomatous pathology** ? Tubercular. AFB stain negative.

EXAMINATION

- General examination –PR – 90 /min; RR- 20 / min ; BP – 130 /80 mmHg.
- Confused agitated - not following commands – with +ve signs of meningeal irritation
- B/L rectus nerve palsy with unequal pupils.
- Brisk reflexes in lower limb & normal upper limb
- Plantar – B/L Extensors

MENINGOENCEHALITIS

Differentials –

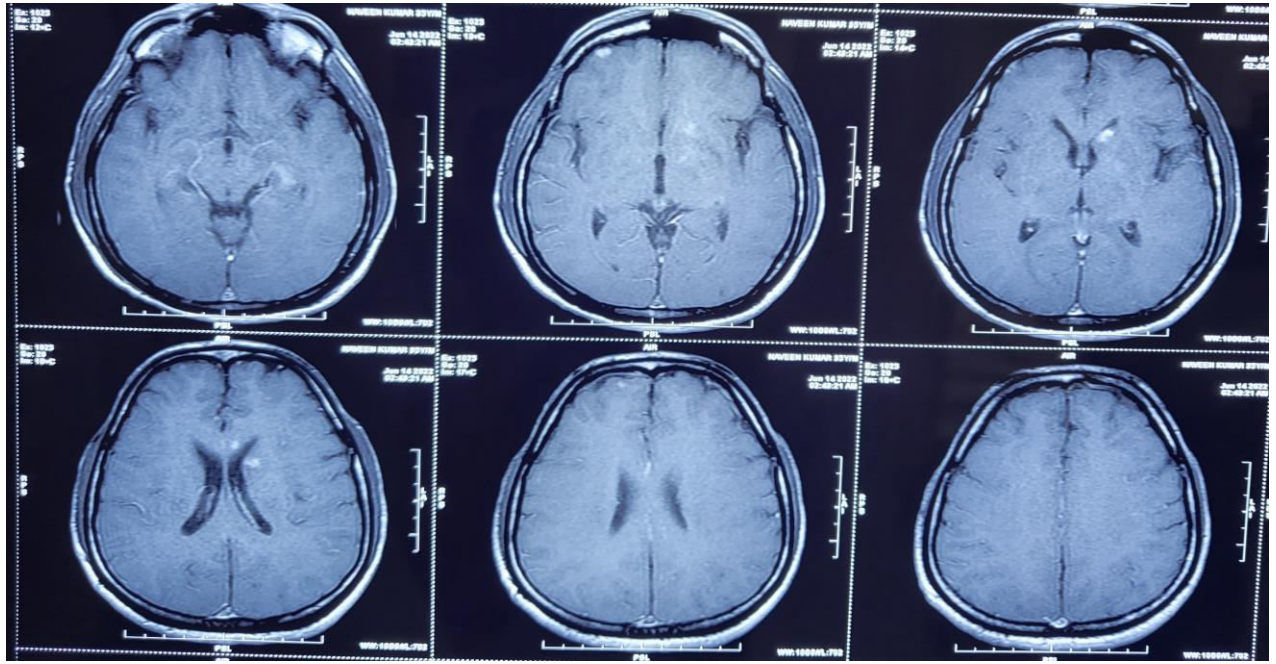
? Tubercular meningitis

? Paradoxical reaction

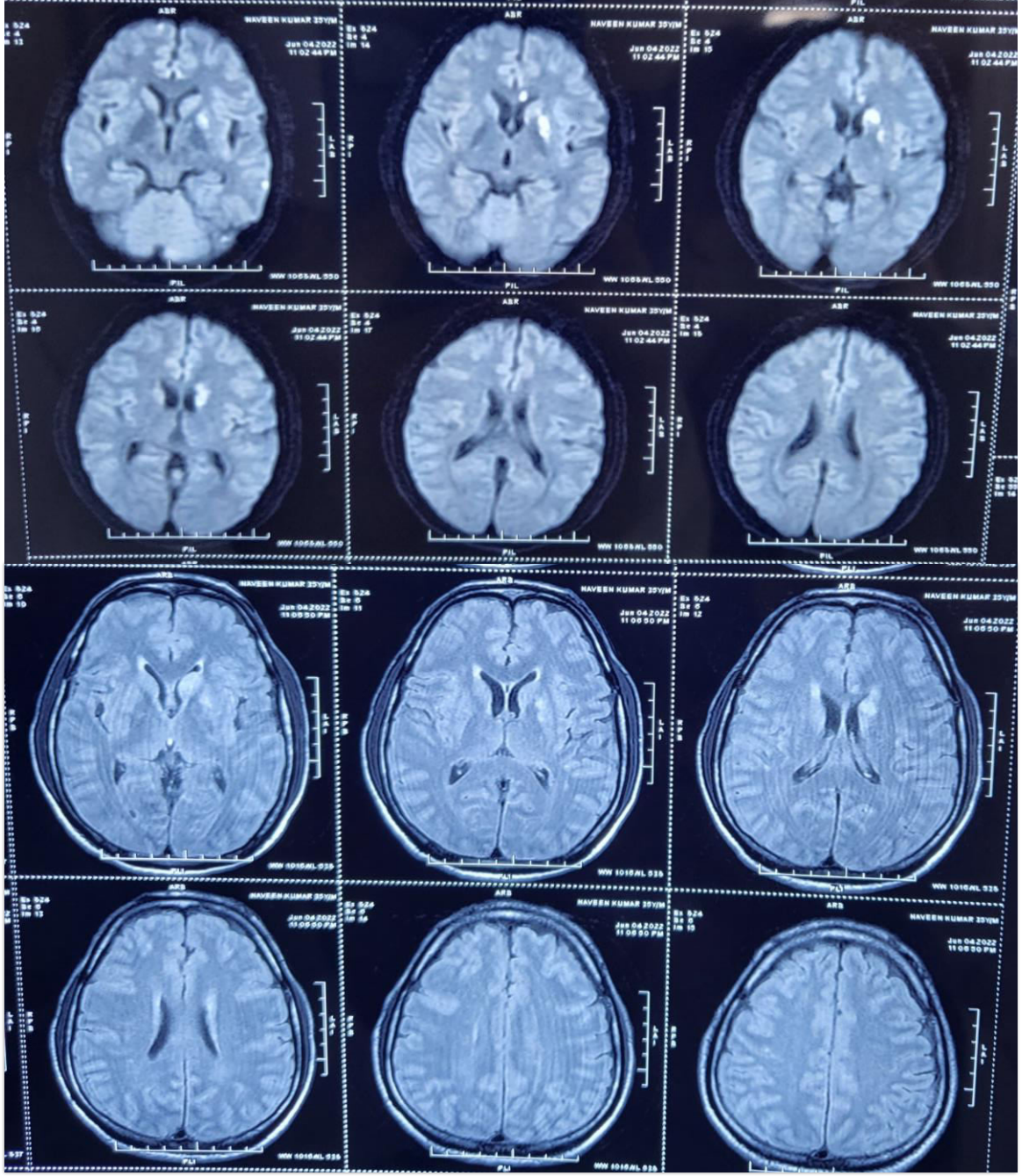
? Bacterial ? Viral ? Fungal

INVESTIGATIONS

Routine – Normal

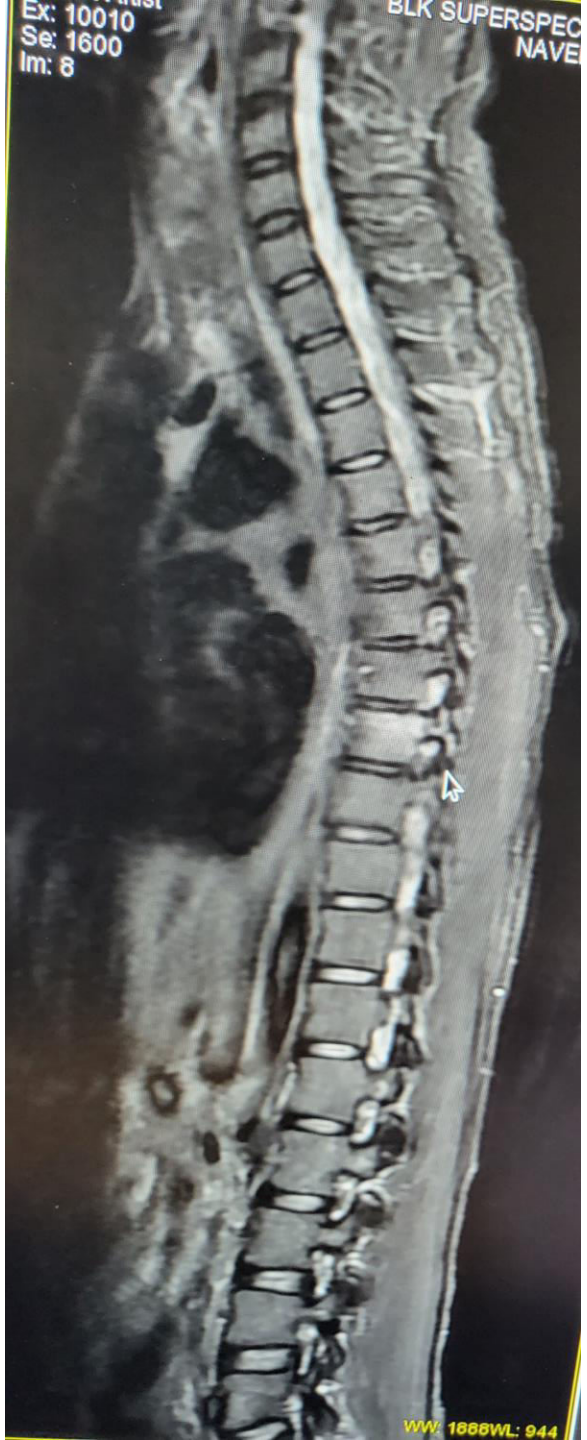


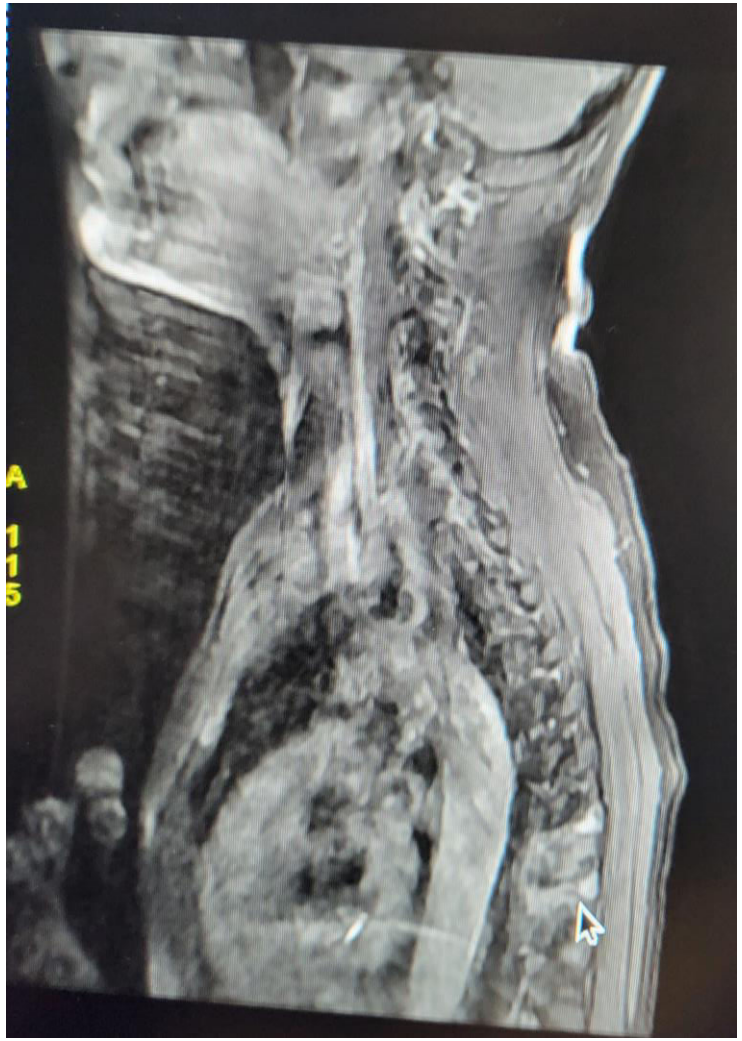
L Basal ganglia contrast enhancement +

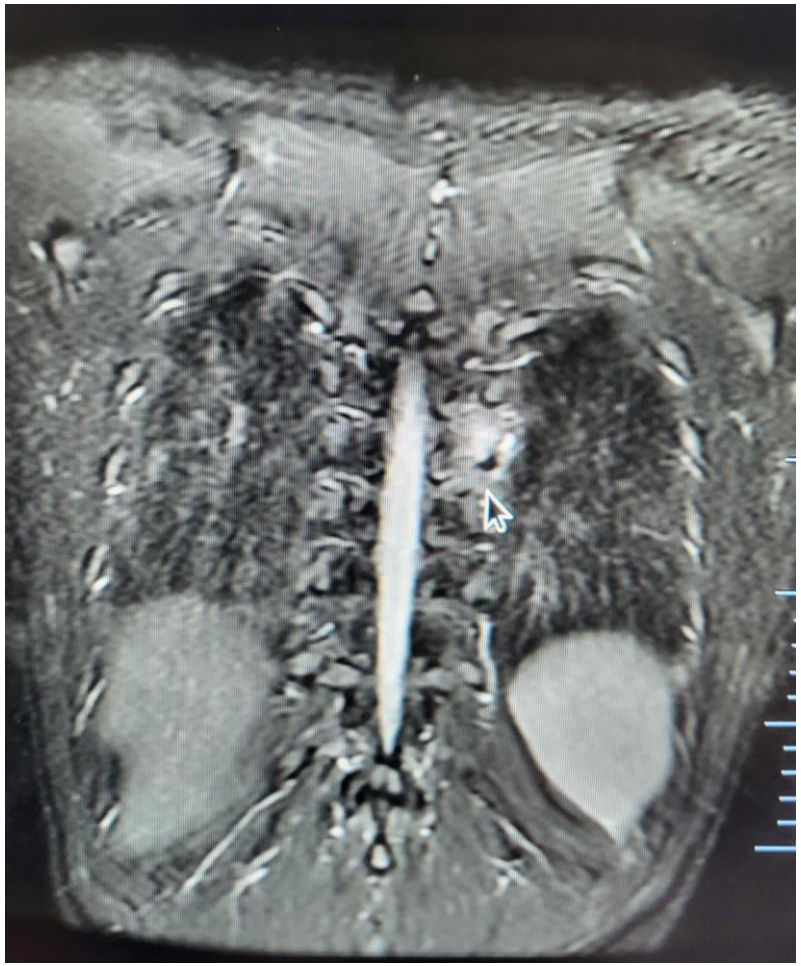


Left basal ganglia, Left frontal DWI alt signal intensity

Heterogeneously enhancing soft tissue 27 x 27 mm at D7-D8 level







SERIAL CSF ANALYSIS

Admission day

Opening pressure – **30** cm H20

Cells – 2

Sugar – 2 mg / dl

Protein – 288 mg /dl

Gene xpert – ve

India ink – ve

Day - 14

Opening pressure – 18 cm H20

Cells – 5

Sugar - 6.3 mg/dl

Protein – 159 mg/dl

Gene xpert – ve

India ink – ve

4 weeks

Cells – 7

Sugar – 37.5 mg/dl

Protein – 146 mg/dl

Gene expert – ve

India ink + cryptococcus

Liposomal amphotericin B + flucytosine

CRYPTOCOCCUS +

Test Name	Result
BIOFIRE - CNS PANEL, Cerebrospinal Fluid Method: Multiplex PCR	
Bacteria	
Escherichia Coli k1	Not Detected
Haemophilus influenzae	Not Detected
Listeria Monocytogenes	Not Detected
Neisseria meningitidis	Not Detected
Streptococcus agalactiae	Not Detected
Streptococcus pneumoniae	Not Detected
Viruses	
Cytomegalovirus	Not Detected
Enterovirus	Not Detected
Herpes Simplex Virus 1	Not Detected
Herpes Simplex Virus 2	Not Detected
Human Herpes Virus 6	Not Detected
Human parechovirus	Not Detected
Varicella Zoster Virus	Not Detected
Yeast	
Cryptococcus neoformans/gattii	Detected

Microbiology

India Ink Preparation for cryptococcus

Specimen : Cerebrospinal fluid

Result: Occasional encapsulated budding yeast cells resembling Cryptococcus spp. seen.

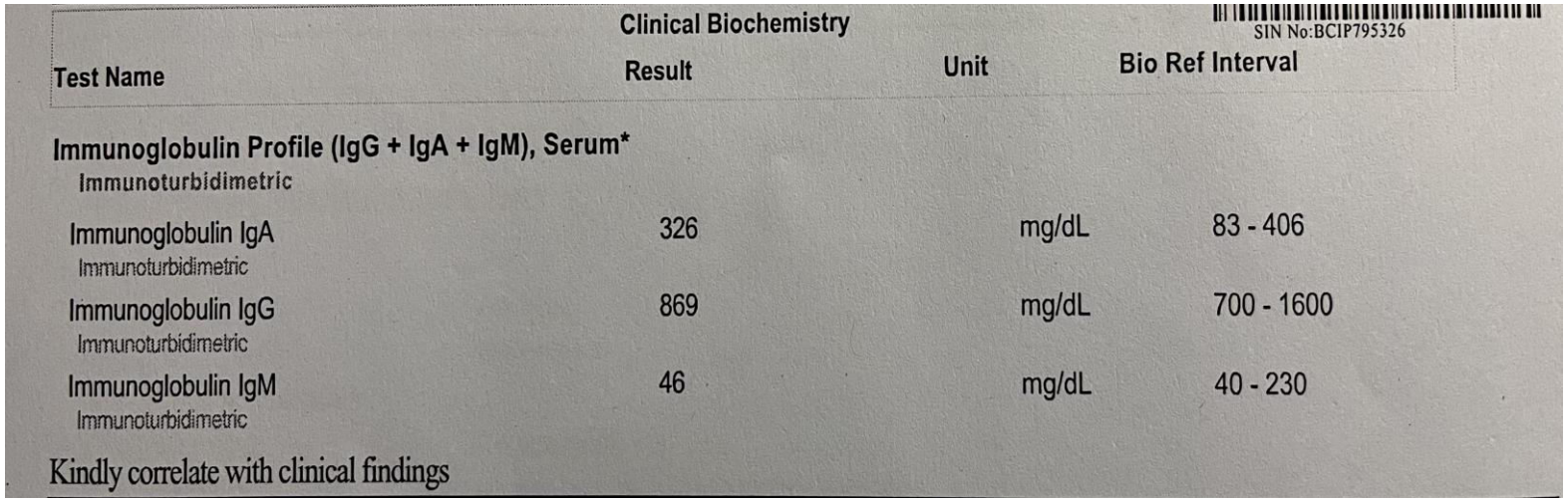
Method: Microscopy

Kindly correlate with clinical findings

BIOFIRE - CNS PANEL, Cerebrospinal Fluid Method: Multiplex PCR	
Bacteria	
Escherichia Coli k1	Not Detected
Haemophilus influenzae	Not Detected
Listeria Monocytogenes	Not Detected
Neisseria meningitidis	Not Detected
Streptococcus agalactiae	Not Detected
Streptococcus pneumoniae	Not Detected
Viruses	
Cytomegalovirus	Not Detected
Enterovirus	Not Detected
Herpes Simplex Virus 1	Not Detected
Herpes Simplex Virus 2	Not Detected
Human Herpes Virus 6	Not Detected
Human parechovirus	Not Detected
Varicella Zoster Virus	Not Detected
Yeast	
Cryptococcus neoformans/gattii	Not Detected

IMMUNE SYSTEM ANALYSIS

- Viral marker & HIV serology – non reactive
- HIV Viral load - negative
- Crytococcal antigen dilution – positive 1:2560
- Dihydrorhodamine (DHR) flow cytometry – 100% neutrophil

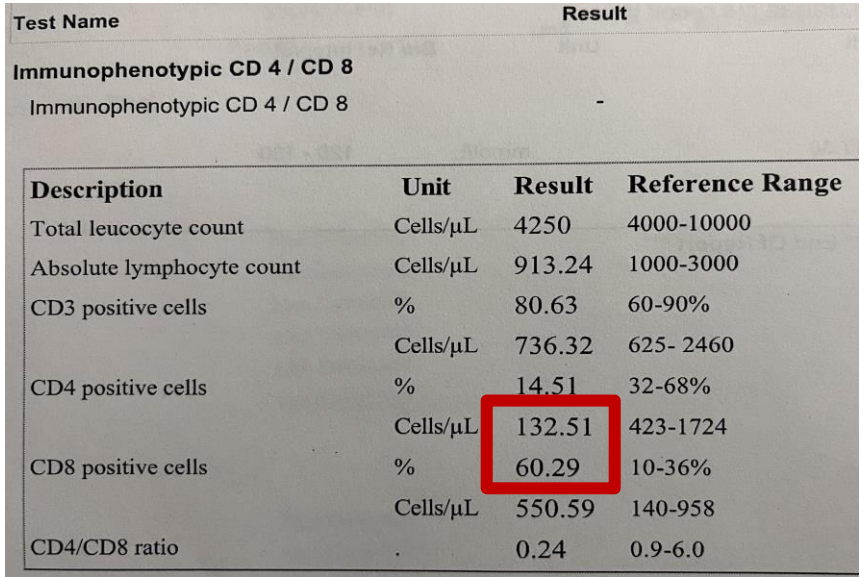


Clinical Biochemistry

SIN No:BCIP795326

Test Name	Result	Unit	Bio Ref Interval
Immunoglobulin Profile (IgG + IgA + IgM), Serum*			
Immunoturbidimetric			
Immunoglobulin IgA	326	mg/dL	83 - 406
Immunoturbidimetric			
Immunoglobulin IgG	869	mg/dL	700 - 1600
Immunoturbidimetric			
Immunoglobulin IgM	46	mg/dL	40 - 230
Immunoturbidimetric			

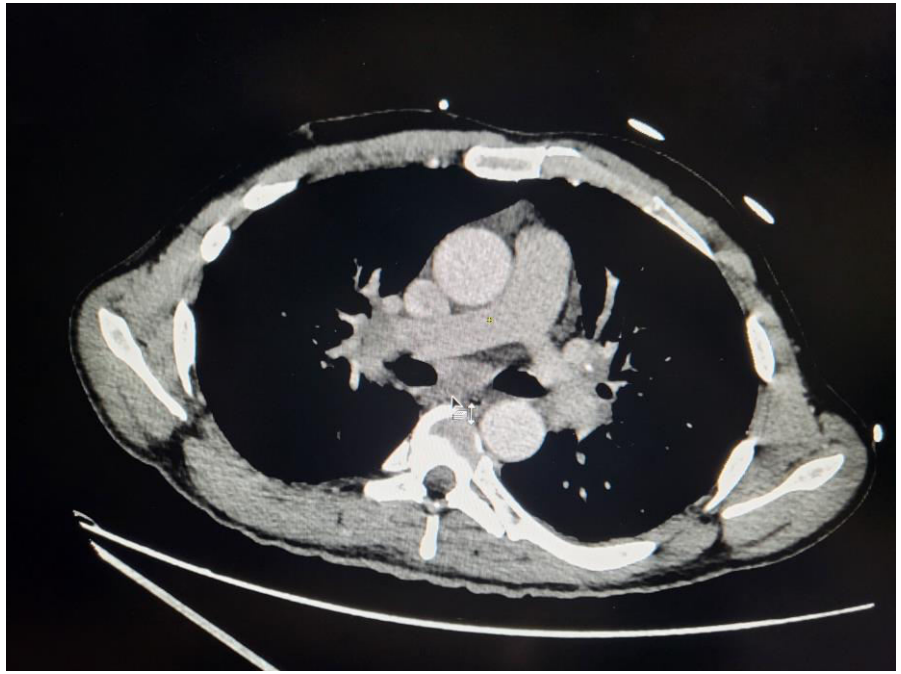
Kindly correlate with clinical findings

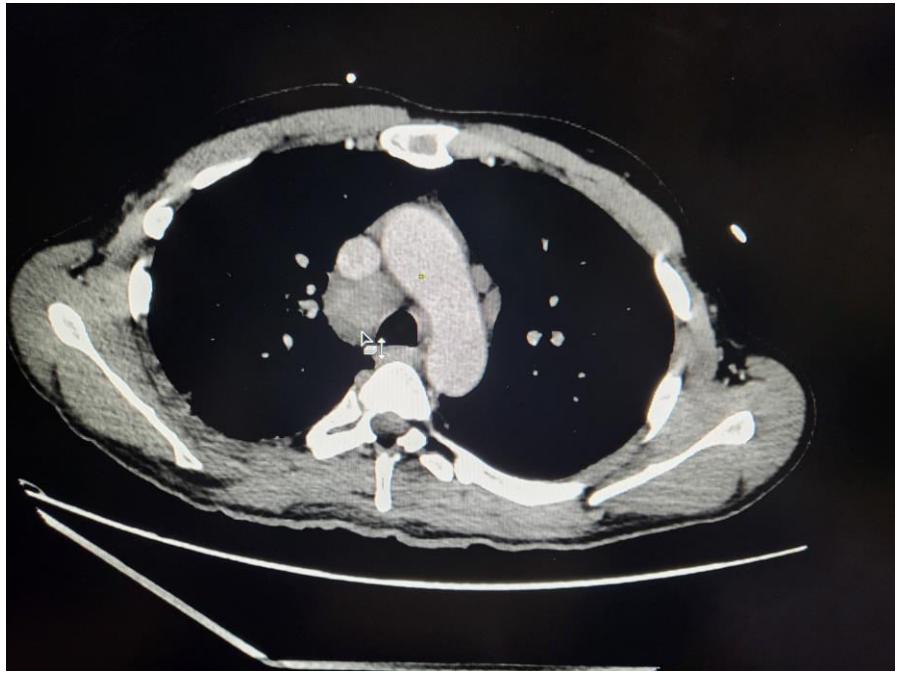


Test Name		Result	
Immunophenotypic CD 4 / CD 8			
Immunophenotypic CD 4 / CD 8		-	
Description	**Unit**	**Result**	**Reference Range**
Total leucocyte count	Cells/µL	4250	4000-10000
Absolute lymphocyte count	Cells/µL	913.24	1000-3000
CD3 positive cells	%	80.63	60-90%
	Cells/µL	736.32	625- 2460
CD4 positive cells	%	14.51	32-68%
	Cells/µL	132.51	423-1724
CD8 positive cells	%	60.29	10-36%
	Cells/µL	550.59	140-958
CD4/CD8 ratio	.	0.24	0.9-6.0

INVESTIGATIONS

- CECT chest - Large right paratracheal lymphnode is seen measuring upto 28x30mm, multiple enlarged mediastinal LN





HISTOPATHOLOGY

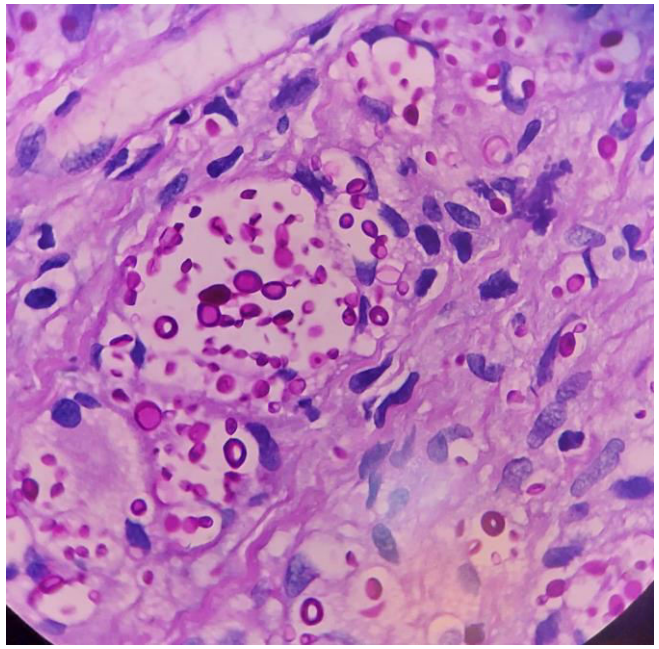
AFB (MYCOBACTERIUM) CULTURE ONLY

Specimen	Aspirate
Source	Lymph node
Microscopy Examination	
AFB Stain Result	No acid fast bacilli seen.
First Week	No growth detected at end of first week
Second Week	No growth detected at end of second week.
Third Week	No growth detected at end of third week.
Fourth Week	No growth detected at end of fourth week.
Fifth Week	No growth detected at end of fifth week.
Sixth Week	No growth detected at end of sixth week.
Seventh Week	No growth detected at end of seventh week.
Eighth Week	No growth detected at end of eight week.

Kindly correlate with clinical findings

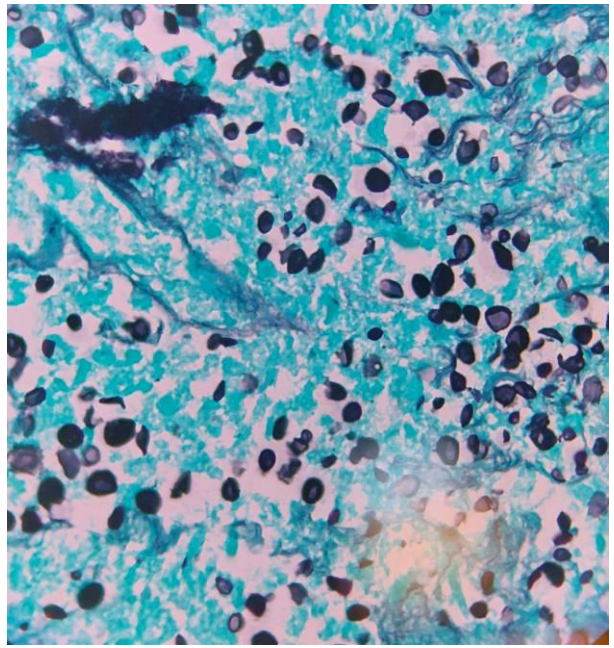
Lung & paravertebral biopsy

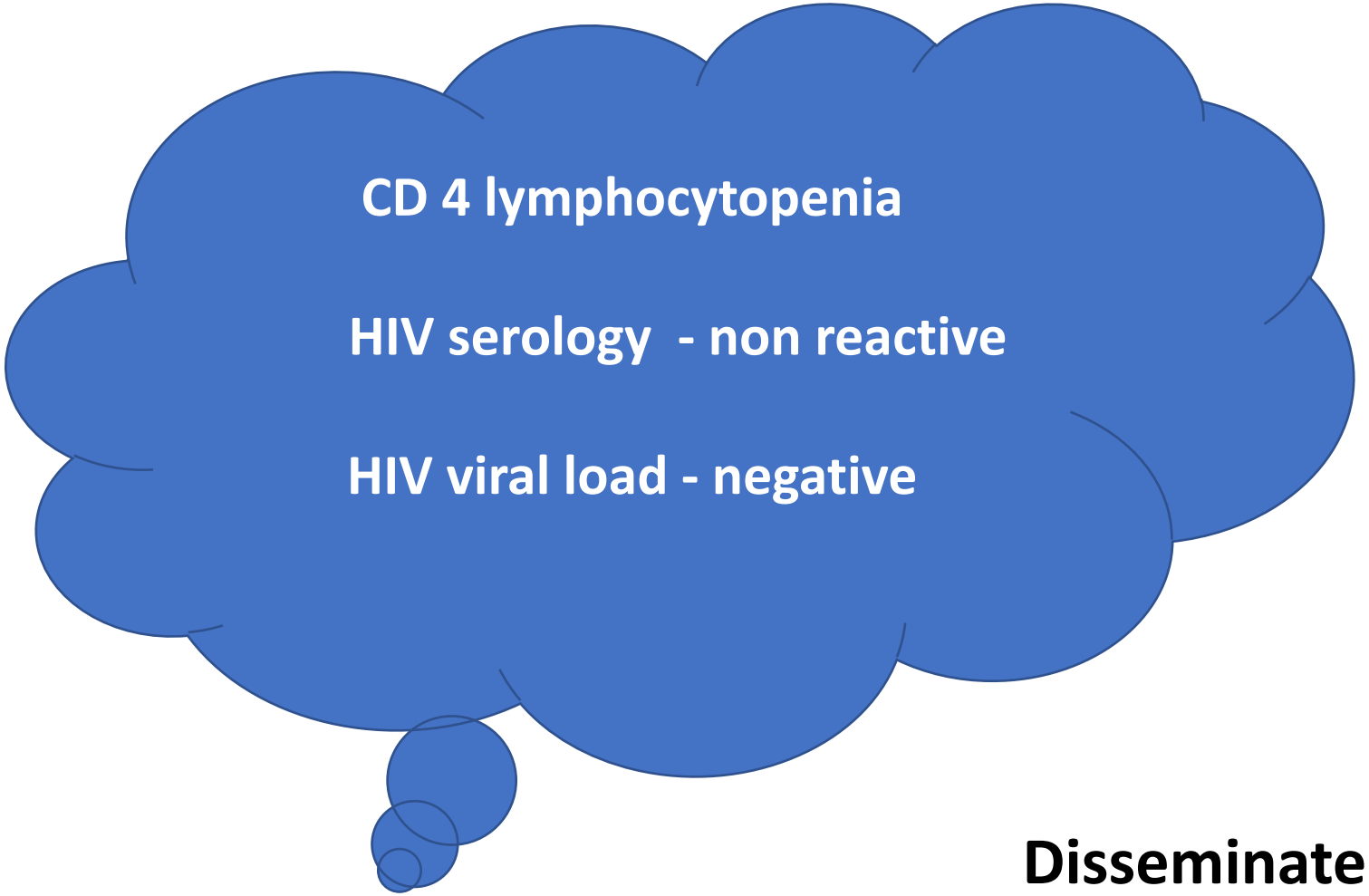
- ***No AFB seen, Gene xpert - negative , AFB culture - Sterile***
- Culture (paravertebral tissue) - **Cryptococcus neoformans**
  - S Amph B, Flucytosine
- Mediastinal LAP slides (outside) rechecked & reported to have granulomatous inflammation with no AFB and cryptococcus.



Yeast like organism surrounded by clear halo In PAS and GMS stain

CRYPTOCOCCUS





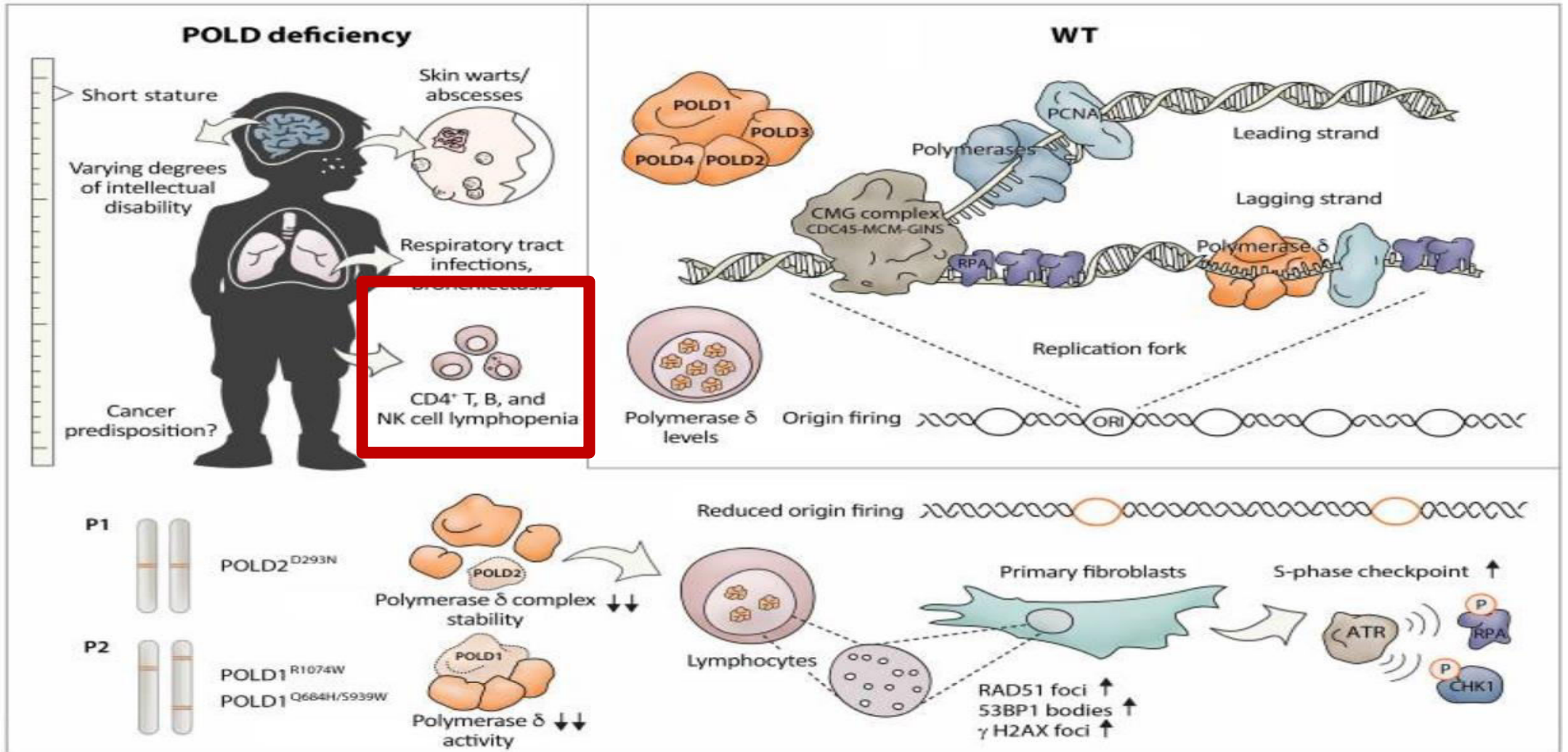
Disseminated cryptococcal infection…

WHOLE EXOME SEQUENCING – POLD 1 MUTATION

*Correlation with clinical profile and family history is required.

FINDINGS RELATED TO PHENOTYPE

Gene & Transcript	Variant	Location	Zygosity	Disorder (OMIM)	Inheritance	Classification
POLD1 NM_002691.4	c.191G>A (p.Gly64Glu)	Exon 2	Heterozygous	Mandibular hypoplasia, deafness, progeroid features, and lipodystrophy syndrome (615381)	Autosomal Dominant	Uncertain Significance



FINAL DIAGNOSIS

- Disseminated cryptococcal infection
- Isolated CD 4 lymphocytopenia secondary to POLD 1 Hetrozygous mutation

TREATMENT

- ATT (HRZ + Moxiflox + STM) - stopped
- Induction phase - Amphotericin B 3 mg/kg + Flucytosine 1000 mg QID
- Inj Ceftriaxone 2 g IV BD + Symptomatic Treatment

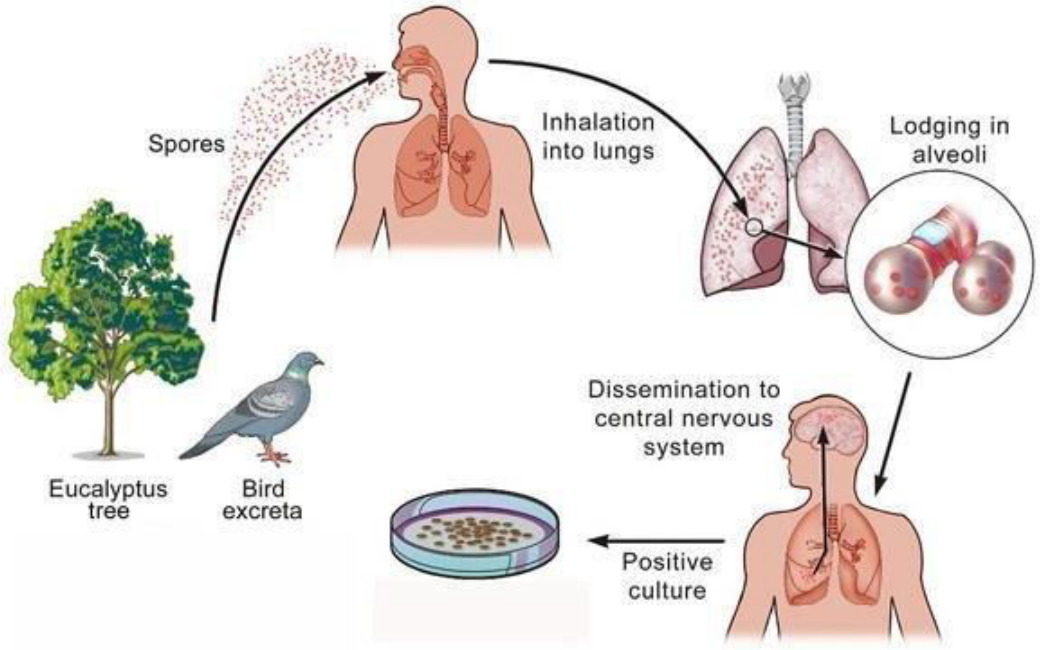
FOLLOW UP

- Maintainance phase – fluconazole 800 mg / day

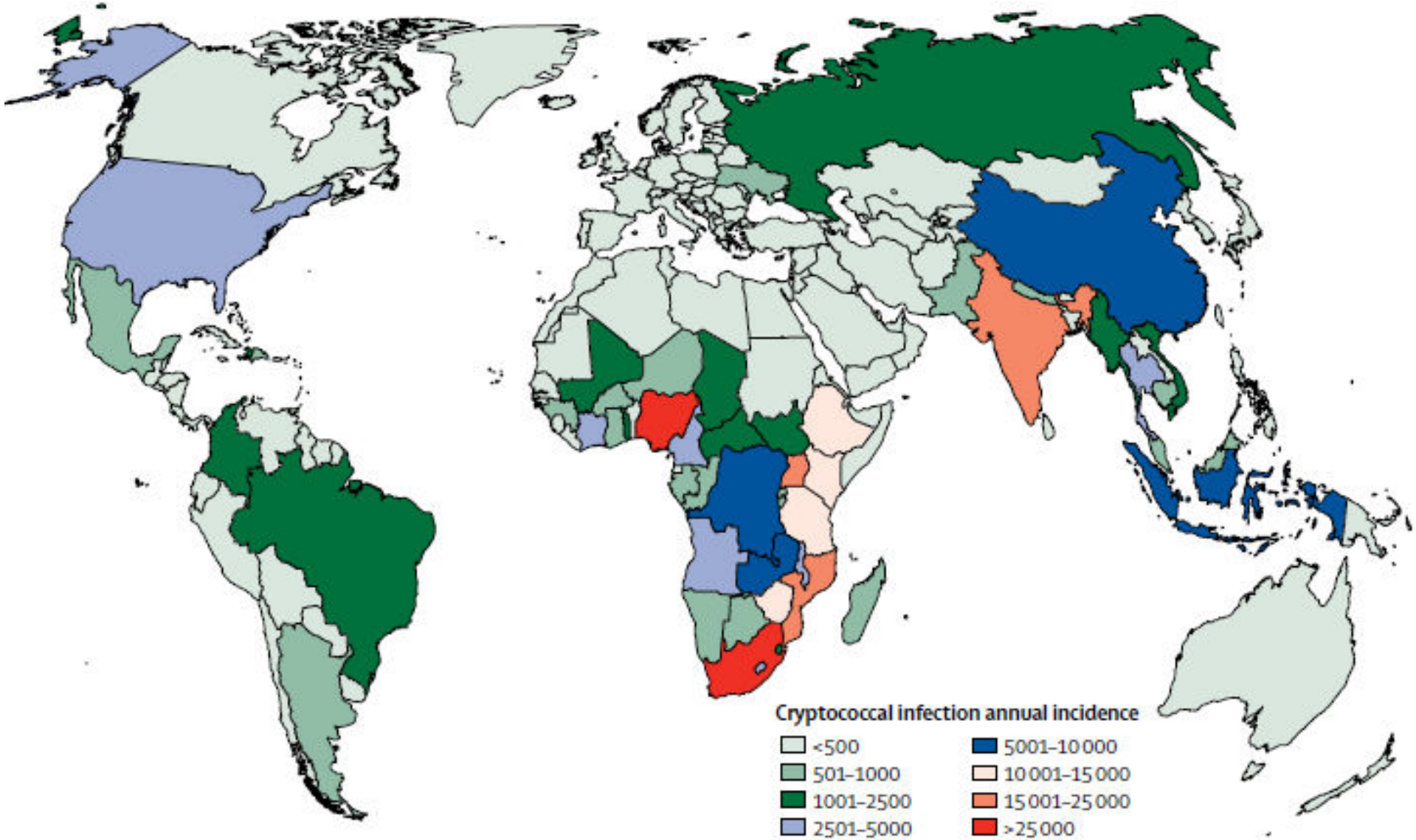
- Weight gain – 12 kgs over 3 months

DISCUSSION

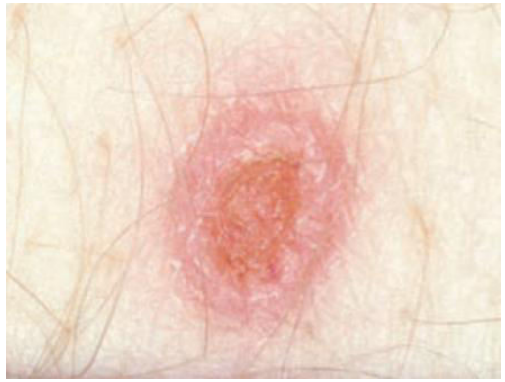
- Suspectedly clinically in patients with sub acute onset
- Meningoencephalitis is the most frequently encountered manifestation of cryptococcosis
- Disease of the **IMMUNOCOMPROMISED**
- 30 percent - no apparent underlying condition.

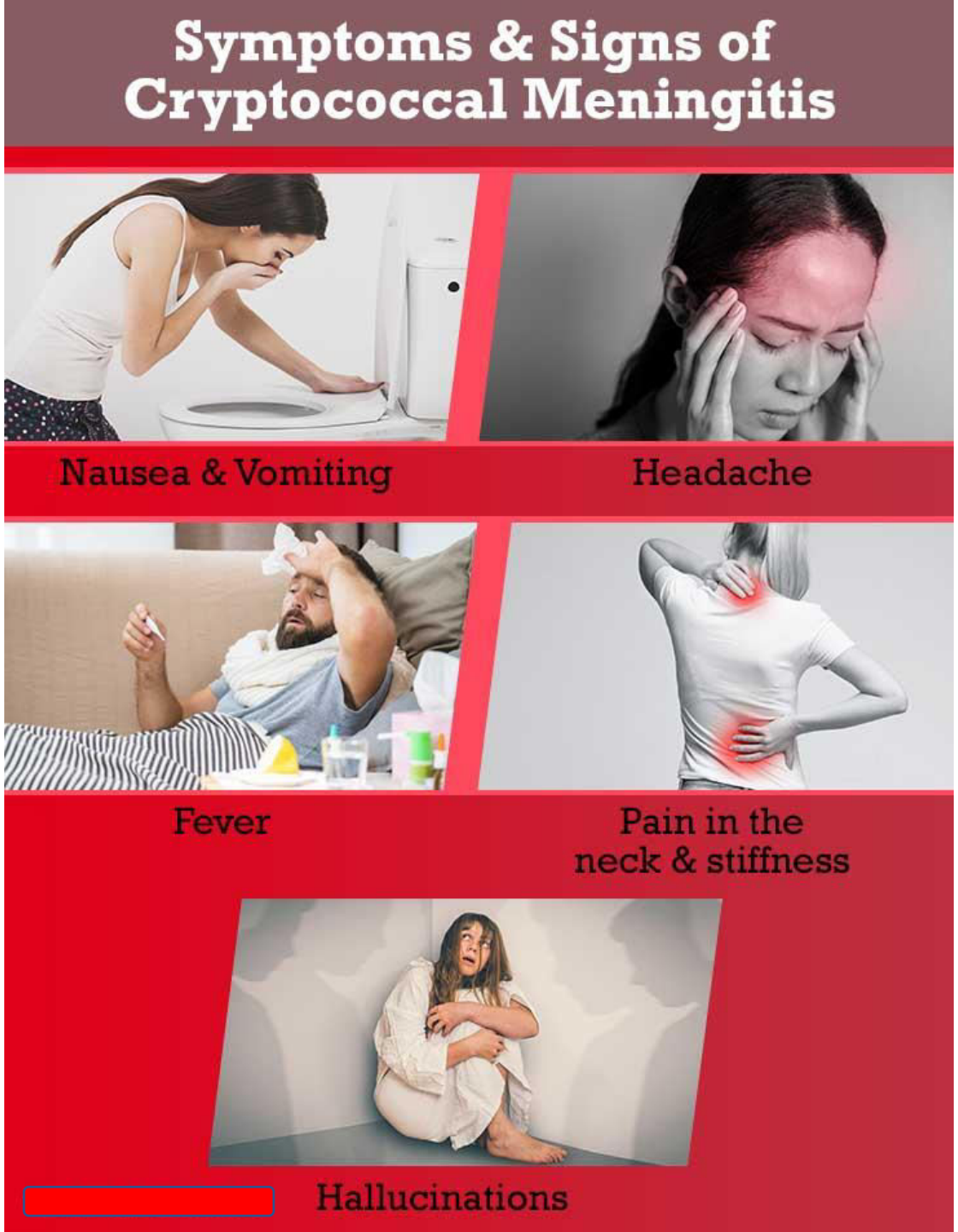


ANNUAL INCIDENCE OF CRYPTOCOCCOSIS



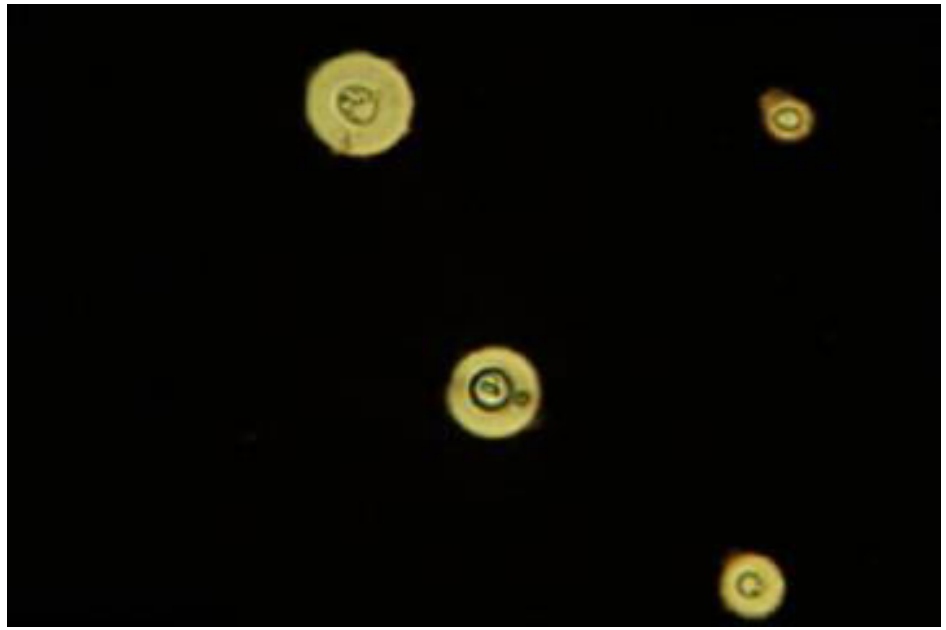
- Subacute
- Pulmonary cryptococcosis
- Granulomatous pulmonary masses – cryptococcomas
- Skin - papules, plaques, purpura, vesicles, tumor-like lesions, and rashes





DIAGNOSIS

- Opening pressure > 20 cm H20- 70%
- Mononuclear predominance; Cell count is lower in **HIV (0-50 cells/uL)** patients than HIV seronegative (**20-200 cells/uL)**
- **Low glucose levels & elevated protein**
- **India Ink** + 75% - HIV to 50% in seronegative.
- Prominent clear zone around individual yeast
- **Cryptococcal PCR-** HIV infection >90 % sensitivity and specificity



LABORATORY MONITORING FOR FUNGAL INFECTION

- Sterilization of CSF – LP repeat after 2 weeks
- Serum CrAG not useful
- Restart maintenance doses of fluconazole in asymptomatic patients immunocompromised:
  - CrAg becomes detectable
  - ≥4-fold rise in the CrAg titer compared with the end-of-treatment level
- Therapeutic LP/ VP shunt

POOR PROGNOSTIC FACTOR

- Abnormal mental status (due to encephalitis and/or increased intracranial pressures)
- CSF assay +ve for yeast cells on initial India ink examination (evidence of a heavy fungal burden)
- High CSF pressure
- Low CSF glucose levels
- Low CSF pleocytosis
- CSF antigen titer >1:1024 by latex agglutination or >1:4000 by lateral flow assay (LFA) (high burden of yeasts)
- CSF white blood cell count <20/microL (poor host response)

TREATMENT

Cryptococcosis:	
HIV patients	Induction: liposomal amphotericin B + flucytosine x 2 weeks (can use amphotericin B or ABLC); lower/middile income countries: amphotericin B + flucytosine ×1 wk, followed by 1 wk of fluconazole (1200 mg/day, adult) Alternate induction: fluconazole (400-1200 mg/day, adult) + flucytosine ×2 wk Consolidation: oral fluconazole 800 mg/day ×8 wk (minimum) Maintenance/secondary prophylaxis: oral fluconazole 200 mg/day Corticosteroids: not recommended during induction Antiretroviral therapy (ART) initiation: defer for 4–6 wk from start of antifungal treatment
Organ transplant patients	Induction: lipid-formulation amphotericin + flucytosine ×2 wk (minimum) Consolidation: oral fluconazole 400–800 mg/day ×8 wk Maintenance: oral fluconazole 200–400 mg ×6–12 mo
Immunocompetent patients	Induction: amphotericin B/lipid-formulation amphotericin + flucytosine ×4 wk Consolidation: oral fluconazole 400–800 mg/day ×8 wk Maintenance: oral fluconazole 200–400 mg ×6–12 mo

TAKE HOME MESSAGE

- EARLY DIAGNOSIS AND TREATMENT IS ESSENTIAL
- MANAGING PATIENT IS A TEAM EFFORT
- DIAGNOSIS IS NOT MADE BY A SINGLE TEAM ALONE

- **We thank the hematology microbiology pathology interventional radiology, radiology and most importantly our residents, nursing and paramedic staff.**

BLK-MAX
Super Speciality Hospital