A rare case of meningitis

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Case

A 37 yr old female patient came to emergency department with complaints of:

- Fever with chills
- Severe headache
- Vomiting

} x 7 Days

H/O - Syncope, diplopia, weight loss, loss of appetite
No H/O – Seizure, joint pain, DM, hypertension

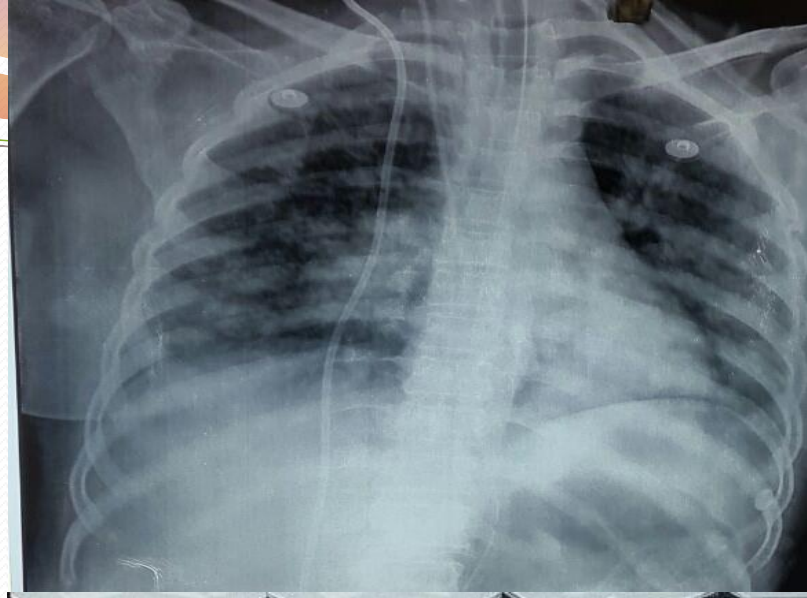
O/E-

- Patient was drowsy, afebrile
- Pulse – 64/min
- BP – 100/60 mm of Hg
- Neck rigidity - **present**
- Kernig's sign - absent
- No focal neurological deficit

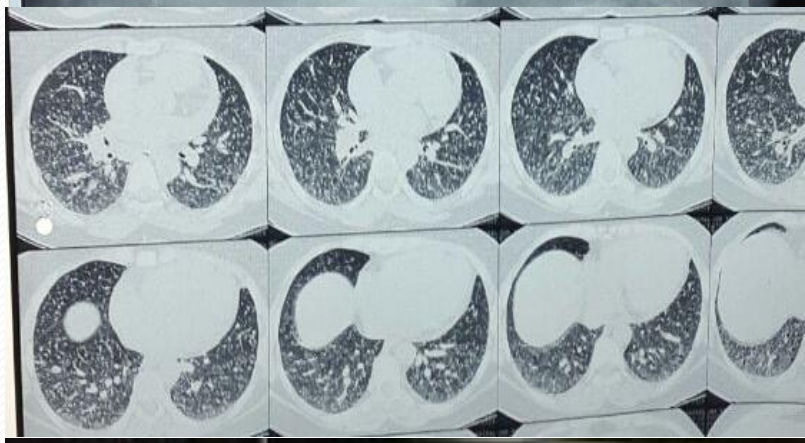
- On further questioning she revealed that she was diagnosed with Miliary TB with Tubercular Meningitis in some private hospital but due to financial reasons she came to our hospital. She also told she had been started on ATT for 2 days.

- As, the patient was drowsy and had slight neck rigidity she was admitted to MICU with a provisional diagnosis of **Miliary tuberculosis with TBM .**

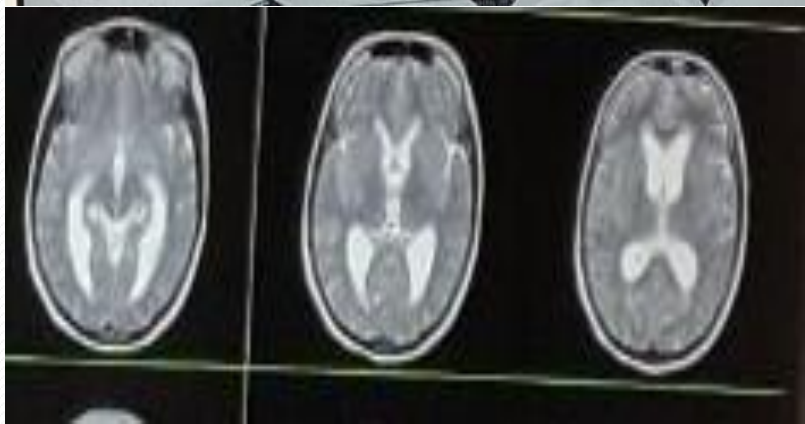
- **Chest X-ray (PA view)** – Right lung consolidation along with multiple miliary nodules in the bilateral lung field



- **CECT thorax –** Diffusely scatered multiple miliary opacities present in bilateral lung field



- **MRI brain-** Dilatation of lateral and 3rd ventricle



Cerebrospinal fluid sent to the Dept. of Microbiology for culture and follow up

- Direct Microscopy of CSF - Acid fast bacilli **NOT** seen on ZN stain
- Total 60 nucleated cells/mm^3 seen (predominantly lymphocytes)

Biochemistry report

- CSF glucose - 44mg/dl
- CSF protein - 480mg/dl

- **Patient was continued on ATT first line in view of clinical signs, symptoms and radiological evidences and further investigations were done.**

First line therapy

Drug	Adult daily dose	Duration (mo)	CNS penitration
Isoniazid	5mg/kg	9-12	Yes
Rifampin	10mg/kg	9-12	Yes, with inflammation
Etionamide	5mg/kg	9-12	Yes, with inflammation
Pyrazinamide	15-30mg/kg	2	Yes
Ethambutol	15-20mg/kg	2	Yes, with inflammation

Patient was also on

- Inj. Dexamethasone,
- Inj. Monocef,
- Inj. Mannitol and
- Inj. Streptomycin

Along with 1st lne ATT drugs

- Patient`s condition was not improving as intended and a 2nd CSF sample was drawn after 20 days and sent for Gene Xpert.

- **GeneXpert - MTB complex detected**

  -Rifampicin resistance detected.(after 21 days)

- Tab levofloxacin was started as a 2nd line drug (after 21 days)

- **Liquid culture: MGIT (Mycobacteria growth indicator tube) – MTB complex grown(after 33 days)**
- **Meanwhile Blood culture reports were–No Growth**

- **Patient was still not responding to the treatment.**

- After 41 days patient was started on Tab cycloserine and next day Inj. Kanamycin was added.

- **LJ Culture report also confirmed growth of MTB.**

- **LiPA report stated: MTB detected with resisitance to both 1st line drugs (Rifampacin and Isoniazid) .** Confirming it as a MDR case.

Discussion

- Pre-extensively drug resistant (pre-XDR) and extensively drug resistant tuberculosis (XDR-TB) have been areas of growing concern, and are posing threat to global efforts of TB control.
- CNS disease caused by MTB is an uncommon yet has highly devastating manifestation of tuberculosis, which was universally fatal in the era before antituberculosis therapy.
- Accounts for approximately 1% of all cases of tuberculosis.
- Due to its relative rarity and the protean nature of the symptoms, it remains a formidable diagnostic challenge.

- MDR TB: Resistant to Isoniazid and Rifampicin
- XDR-TB: defined by resistance to isoniazid, rifampin, fluoroquinolones, and either capreomycin, kanamycin, or amikacin.

- With the emergence of extensively drug-resistant (XDR) tuberculosis even these second-line agents will be ineffective.

- Second-line agents such as ethionamide (which is structurally similar to isoniazid) and cycloserine have good CNS penetration and may be among the only agents available to begin building a treatment regimen for XDR TBM.

How the resistance was detected?

- Growth from solid culture was used for **DNA extraction**

- **Sequencing**-
- **16S r RNA partial sequence**- confirmed as *Mycobacterium tuberculosis*
- **Single nucleotide polymorphism -**
- RIFA– mutation 3 (seq S450L)
- INH – mutation 1 (seq S315T)

GENE	LOCUS	DRUG	CHANGE
gyrA	Rv0006	Fluoroquinolones	GAC/CAC
rpoB	Rv0667	Rifampicin	TCG/TTG
rpsL	Rv0682	Streptomycin	AAG/AGG
katG	Rv1908c	Isoniazid	AGC/ACC
embB	Rv3795	Ethambutol	ATG/GTG

- **Spoligotyping** – Beijing strain

  (Rapid PCR based method for detection of origin of MDR strains of *Mycobacterium tuberculosis)*

- **Whole genome sequencing** – of the strain was done to confirm mutation as PreXDR confirmation and to find any new mutations confering.
- Then strain was found to be resistant to Rifampicin, isoniazid, fluroquinilone, ethambutol and streptomycin.

- With MDR/XDR tuberculosis, time to identification of resistance is often prolonged, and therefore, time to appropriate antituberculosis therapy is delayed(up to 10 weeks) or even initiated after the disease has advanced too far.

- The mortality among these MDR/XDR TBM cases is quite high, many of the patients never actually received adequate therapy prior to their demise.

Summary

- In our case patient had
- C/O- fever, headache
- H/O – miliary TB, TBM
- O/E – neck rigidity was present
- Direct microscopy-NO AFB seen
- **GeneXpert** – MTB complex detected with Rifampicin resistance
- **Liquid culture: MGIT** – MTB complex grown
- **LJ Culture report also confirmed growth of MTB.**

- **LiPA report stated: MTB detected with resisitance to both 1st line drugs (Rifampacin and Isoniazid) - MDR**

Conclusion

- Patients detected with TB having resistance to any of the 1st line drug should be cheked for resisitance to the other drug too.
- Also, in case of MDR strains always the possibility of XDR should be ruled out with the help of LiPA 2nd line.
- As the mortality rates are very high in these cases patient should be investigated and treated judiciously.

Take home message

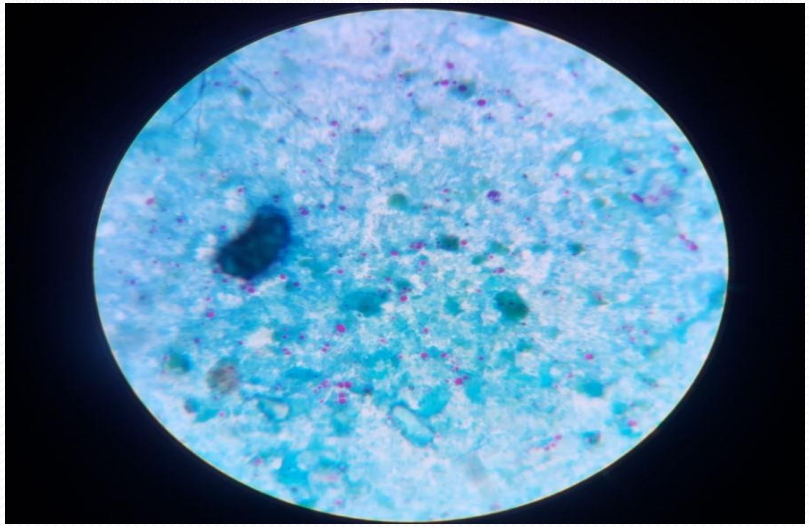
In a deterioting patient with TBM who is on 1st line or 2nd line ,molecular methods like 2nd line LiPA,

should be considered followed by Single gene sequencing or Whole Genome sequencing if needed as mortality is very high in these TBM cases with MDR/XDR strains.

DEPARTMENT OF MICROBIOLOGY ALSO CONTRIBUTED IN DIAGNOSING DIFFICULT CLINICAL CASES PRESENTED BY OTHER DEPARTMENTS.

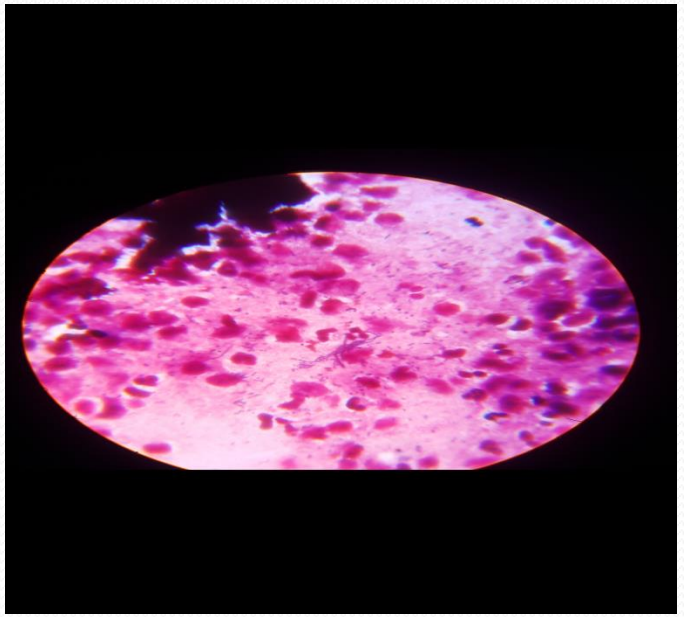
1) Medicine:

HIV Cholangiopathy



2)Pulmonary medicine:

An Unusual Bacterial Infection in Immunocompetent Host



Thank you.