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MIXED MENINGITIS DUE TO *STREPTOCOCCUS PNEUMONIAE AND MYCOBACTERIUM TUBERCULOSIS.*

Microbiology

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ABSTRACT

Meningitis is a medical emergency which needs prompt diagnosis and early initiation of therapy. Meningitis can be aseptic, pyogenic, fungal, parasitic, tuberculous, chemical or mixed type. Here, we report a rare case of mixed meningitis caused by Mycobacterium tuberculosis and Streptococcus pneumoniae in adult female presenting with fever, headache and vomiting for 15 days . Investigations revealed raised Neutrophils(86%), chest X-ray (CXR: suggestive of milliary tuberculosis).On cerebro-spinal fluid (CSF) examination, sugar level was low, protein markedly high, raised Adenosine deaminase (ADA),cytology showed predominantly polymorphonuclear cells and Gram staining showed pus cells with Gram-positive diplococci. India Ink staining using Anthony's method revealed capsulated diplococci, however culture was negative. Patient did not respond well to ceftriaxone and vancomycin. Gene-Xpert detected Mycobacterium tuberculosis but no resistance to rifampicin. Zeihl-Neelsen (ZN) staining of CSF was negative. Patient improved very well after addition of anti- tubercular drugs. Since clinical features do not suffice, even conventional microbiological diagnostic tests like Gram staining & India Ink staining could be crucial in the diagnosis of pyogenic meningitis and prompt initiation of antimicrobial therapy especially in resource poor countries. Rarely pyogenic meningitis may be associated with tuberculous meningitis. Considering high burden of tuberculosis in India, it is wiser to send CSF for ZN staining & Gene Xpert even in proven cases of pyogenic meningitis. Early diagnosis and initiation of anti- tubercular therapy will reduce morbidity and mortality associated with tuberculous meningitis and fulfillment of our dream of "TB MUKT BHARAT".

KEYWORDS

Gene xpert; Mixed meningitis; Mycobacterium tuberculosis; Streptococcus pneumoniae.

Introduction

Mixed meningitis is caused by simultaneous infection of more than one micro-organism. In bacterial meningitis death can occur in a few hours.[1] In 2015, meningitis occurred in about 8.7 million people worldwide resulting in 379,000 deaths.[2] CNS TB in India accounts for an estimated 1% of all cases of TB, which equates to around 17 000 cases in India in 2014 (WHO, 2015). Case fatality rates for the most common form of CNS TB, i.e. TB meningitis, are high. All forms of central nervous system (CNS) TB can leave survivors with long-term disabilities.[6] Mixed meningitis due to pyogenic & tubercular infection is further uncommon and poses diagnostic and management challenges.

A presumptive diagnosis of bacterial meningitis can be made by combination of clinical picture and laboratory examination of the cerebrospinal fluid (CSF) like Gram stain, India Ink stain, latex agglutination test and other rapid diagnostic test (RDT) for specific antigens in CSF. Positive results for any of these tests can rapidly provide evidence of infection, even if cultures fail to grow.[3]

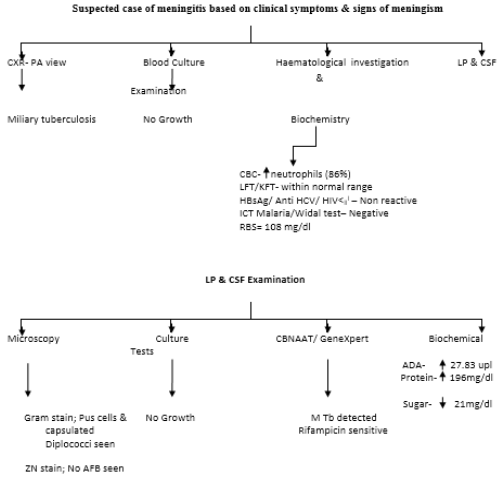
Here, we report a case of mixed meningitis due to *Streptococcus pneumoniae* & *Mycobacterium tuberculosis*.

Case report

A 38 years old lady presented with complaints of fever, headache and vomiting on and off for 15 days. Fever was moderate to high grade, intermittent and associated with chills & rigors with no history of haematemesis, cough, burning micturition or any chronic medical or surgical illness. Patient had fever 2 months back which was treated by local practitioner. Again she has been taking medicines from locally available practitioners but gradually increasing malaise, weakness, loss of appetite and body weight reduction brought her to this hospital. On examination, patient was febrile & pale. CNS examination revealed signs of meningism with general and systemic examinations being normal.

On investigation complete blood count (CBC) revealed neutrophilia (86%), RBS-108 mg/dl with LFT, KFT within normal limits. CSF was turbid and Gram staining microscopy revealed many pus cells and Gram- positive, diplococci (figure 1). India Ink staining using Anthony's method[4] revealed capsulated diplococci (figure 2).CXR was suggestive of miliary tuberculosis. CSF protein level was markedly raised (196mg/dl; reference value being >45 mg/dl), sugar was reduced (21mg/dl; reference being<45 mg/dl), ADA value was 27.83u/l (normal range <10u/l, positive>10u/l),ICT Malaria & Widal test were negative. Based on Gram stain & India Ink staining it was diagnosed as a case of bacterial meningitis. Patient was put on Ceftriaxone and Vancomycin empirically. However, patient did not respond well to the desired level. There was no yield on culture made on blood agar, chocolate agar & MacConkey agar. Later on Xpert MTB/RIF assay (Gene Xpert test) detected *Mycobacterium tuberculosis* (figure 3) but no rifampicin resistance was detected. Patient was diagnosed as a case of mixed meningitis due to *Streptococcus pneumoniae* & *Mycobcaterium tuberculosis.* Patient responded well to addition of antituberculous drugs. Patient was discharged after recovery.

Algorithm of diagnosis of the case:-



India Ink- Capsulated diplococci seen (Anthony's Method)
ICT – Immuno Chromatography Test , CBC – Complete Blood Count
CXR – Chest X-ray,
RBS – Random Blood Sugar
KFT – Kidney Function Test
LFT – Liver Function Test
LP – Lumbar Puncture
ADA – Adenosine Deaminase
AFB- Acid fast bacilli

Discussion

Meningitis is a medical emergency requiring urgent diagnosis and initiation of therapy. It can be due to infectious or non infectious reasons. Infectious causes include bacteria, viruses, fungi and parasites either singly or mixed. *Mycobacterium tuberculosis* has also been implicated in meningitis especially in countries with the high burden of tuberculosis.

About one-third of the world's population has Latent TB which means that persons are infected with *Mycobacterium tuberculosis* but do not have signs or symptoms of the disease. These infected people have a 10% lifetime risk of falling ill with TB.[5] *Mycobacterium tuberculosis* may be the sole agent or rarely associated with other bacteria in meningitis. Mixed meningitis has been reported since the 1990by several workers .[1] Tuberculosis remains a major public health problem in India. Case fatality rates for the most common form of CNS TB, i.e. TB meningitis, are high.

Prompt and accurate diagnosis of meningitis is a challenging task. Clinical symptoms and signs are not sufficient to reach the specific diagnosis. Laboratory confirmation is essential to know the exact cause of the disease. CSF should be subjected to a battery of tests-[6] Cell count and differentiation, Protein, serum glucose ratio, Gram stain for bacterial meningitis , ZN stain for TB, India Ink and cryptococcal antigen testing for cryptococcal meningitis, Xpert MTB/RIF, bacterial, fungal & Mycobacterial - culture, speciation and drug susceptibility testing .

The Xpert MTB/RIF assay is a cartridge based nucleic acid amplification test (CBNAAT), automated diagnostic test that can identify *Mycobacterium tuberculosis* (MTB) and resistance to rifampicin (RIF). WHO recommends that Xpert MTB/RIF should be used rather than conventional microscopy, culture and DST as the initial diagnostic test in adults suspected of having MDR-TB or HIV associated TB.[7]

In our patient, Gram stain of CSF revealed the presence of pus cells & Gram-positive, diplococci. Several studies have reported Gram staining as the most useful single test for identifying bacterial meningitis, as it revealed more positive cases than cultures.[8] CSF Gram stain has sensitivity of 60-90% and a high specificity of >97%, stressing its importance in the rapid diagnosis of the causative bacteria.[9] Culture-negative cases of meningitis or a low CSF culture positivity, ranging from 6-50% has been reported across India. Failure of growth of organism on culture could be attributed to many factors.[10] In our case, the reason for negative culture seems to be antibiotic treatment taken on & off from locally available practitioners before coming to this hospital.

CONCLUSION

Early diagnosis of pyogenic meningitis can be reached with the use of conventional microbiological tests like Gram stain, India Ink stain of CSF & routine blood tests like CBC, RBS, especially in peripheral hospitals. In cases not responding adequately to antibiotics, tuberculous meningitis (TBM) could be a probability considering the high burden of tuberculosis in our country. Although rare but simultaneous occurrence of TBM must be ruled out as it is associated with long term disability and sequelae. This simple step can have a major impact in reducing the disability due to tuberculosis and big leap in the direction of realizing the vision of **TB-Free India with zero deaths, disease and poverty due to tuberculosis by 2025.**

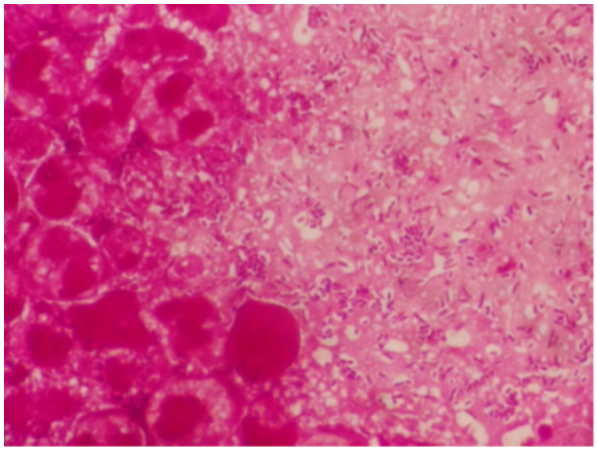


Figure 1: Gram stain of CSF showing Gram –positive, lanceolate, capsulated diplococci.

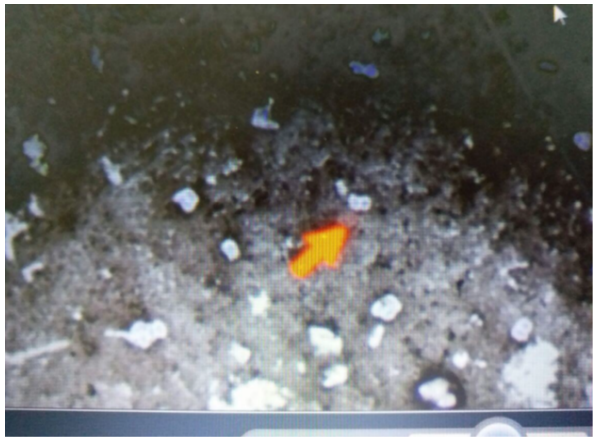
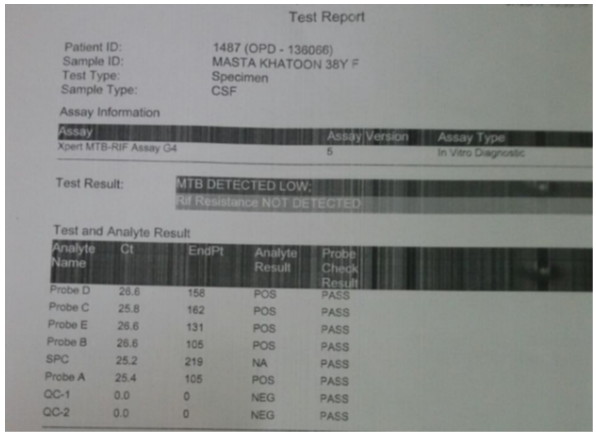


Figure 2: India Ink stain(Anthony's method) showing capsulated diplococci



Test Report

Patient ID: 1487 (OPD - 136066)
Sample ID: MASTA KHATOON 38Y F
Test Type: Specimen
Sample Type: CSF

Assay Information

Assay	Assay Version	Assay Type
Xpert MTB-RIF Assay G4	5	In Vitro Diagnostic

Test Result: MTB DETECTED LOW
Rif Resistance NOT DETECTED

Test and Analyte Result

Analyte Name	Ct	EndPt	Analyte Result	Probe Check Result
Probe D	28.6	158	POS	PASS
Probe C	25.8	162	POS	PASS
Probe E	26.6	131	POS	PASS
Probe B	26.6	105	POS	PASS
SPC	25.2	219	NA	PASS
Probe A	25.4	105	POS	PASS
QC-1	0.0	0	NEG	PASS
QC-2	0.0	0	NEG	PASS

Figure 3: Gene Xpert report of CSF.

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