Abstract:
Mycobacterium tuberculosis infecting central nervous system is quite common in our country, here we are presenting a case of TB meningitis (HIV ELISA-negative), who was started on ATT, but continued to develop tuberculoma which increased in size and number when on ATT, also developed radiculomyelitis when on ATT which are possibly attributed to a PARADOXICAL REACTION to ATT initiated for TB meningitis. These manifestations subsided on re-introduction of steroids and continuation of ATT, along with supportive measures.

Keyword: TB-meningoencephalitis, Paradoxical reaction, Radiculomyelitis, Tuberculoma, ATT

INTRODUCTION:
Tuberculosis infection is classified as pulmonary, extrapulmonary, or disseminated. Tuberculosis of CNS accounts for 5-10% of extrapulmonary cases and 10-30% intracranial masses are tuberculomas. [1] It is seen most often in young children but also develops in adults, especially in immunocompromised individuals. CNS Tuberculosis includes Tuberculous Meningitis, Tuberculous Arachnoiditis, Tuberculoma, and Tuberculous Abscess. Tuberculous meningitis results from the hematogenous spread or from the rupture of a subependymal tubercle (RICH FOCUS) into the subarachnoid space. The disease often presents subtly as headache and slight mental changes. If not recognized, tuberculous meningitis may evolve acutely with severe headache, confusion, lethargy, altered sensorium, and neck rigidity. Typically, the disease evolves over 1–2 weeks, a course longer than that of bacterial meningitis. The ultimate evolution is toward coma, with hydrocephalus and intracranial hypertension. Lumbar puncture is the cornerstone of diagnosis. Acid Fast Bacilli are seen on direct smear of CSF sediment in up to one-third of the cases. Culture of CSF is diagnostic in up to 80% of cases and remains the gold standard. Polymerase chain reaction (PCR) has a sensitivity of up to 56-90%, and specificity of 88-100%. [2] The ADA concentration may be contributory with a sensitivity of 83% and specificity of 95%. [3] If unrecognized, tuberculosis meningitis is uniformly fatal.
This disease responds to chemotherapy; however, neurologic sequelae are documented in 25% of treated cases, in most of which the diagnosis has been delayed. Clinical trials\[^4\] have demonstrated that patients given adjunctive glucocorticoids may experience faster resolution of CSF abnormalities and elevated CSF pressure, significantly enhanced the chances of survival among persons >14 years of age but did not reduce the frequency of neurologic sequelae. Tuberculosis, an uncommon manifestation of CNS tuberculosis, presents as one or more space-occupying lesions and usually causes seizures and focal signs. CT or MRI reveals contrast-enhanced ring lesions, but biopsy is necessary to establish the diagnosis.

**CASE SUMMARY:**

Ismail, a 23 year old male admitted with fever on and off for 1 month and acute onset altered sensorium, not associated with seizure activity. On examination, his BP was 110/70 mmHg, Pulse-64/min. He was disoriented with signs of meningeal irritation and had no focal neurological deficits. Basic investigations showed Blood sugar -110mg/dl, complete blood count-normal, liver function tests-normal, Blood urea-38mg/dl, Serum creatinine-0.9mg/dl. MSAT, MP-QBC, Blood WIDAL were Negative, VDRL-Non reactive, ELISA HIV I & II-Non reactive. ECG showed Sinus bradycardia. CXR PA view and USG Abdomen was Normal. Mantoux test was Negative. CSF Analysis showed Sugar – 13mg/dl, Protein – 155.8mg/dl, TC – 60 cells, DC – Predominant Lymphocytes, Gram stain, AFB – negative, C/S – No growth, Cytology – Inflammatory smear, ADA – 16.75, features suggestive of TB meningitis.

**Diagnosis of TB meningoencephalitis was made and patient started on ATT (HRZS: Isoniazid 5mg/kg, Rifampicin 10mg/kg, Pyrazinamide 25mg/kg, and Streptomycin 15mg/kg, as per WHO 2010 guidelines) along with steroids (Inj. Dexamethasone 8 mg iv BD)**

Patient showed good clinical improvement was discharged and advised to continue ATT along with prednisolone 60 mg , to be tapered over 8 weeks. He was strictly adherent to the drugs.

**CT brain contrast: Contrast ring enhancing hypo dense lesion 2 * 2 cm in R parietal lobe with surrounding edema**

During the third month of ATT, Patient developed one episode of seizure (GTCS). Patient was admitted again and on examination revealed, patient was in post-ictal state, a possible diagnosis of seizures secondary to tuberculosis was made.

**CT result: Active Granuloma R parietal lobe (Tuberculoma).** ATT was continued and T. Phenytoin 100 mg 2 HS was added and patient was discharged with the above advice. He was on regular medications. During the fifth month of ATT, Patient developed inability to initiate urination, difficulty in passing stools, weakness of lower limbs. General and systemic examination revealed MMSE – 23/30, cranial nerve examination was normal, and power of 4/5 in both lower limbs, and DTR were absent, sensory involvement below L1 level and a clinical diagnosis of spinal radiculomyelitis.
CT (Plain & Contrast) was taken, showed - **Multiple ring enhancing lesions** in the R temporal lobe, R frontal lobe and L parietal lobes with mild peri-lesional edema. Increase in size of the lesion.

CT brain contrast showing ring enhancing lesion right frontal and temporal lobe
Repeat investigations showed: Normal CBC & RFT, ELISA for HIV I &II – negative, WIDAL Negative, MSAT-Negative, IgM Dengue Ab-Negative, VDRL- Negative, Peripheral smear was normal.

**ELISA for HIV I &II – negative.** USG Abdomen – Normal study TORCH PANEL – negative CSF
ANALYSIS: Sugar – 53 mg/dl, Protein – 75 mg/dl, Cytology – acellular smear, Cell count – 54 cells/mm$^3$ predominant lymphocytes. ADA – 3 (not significant). Cob Web was Negative.

**CSF PCR was negative for mycobacterium; MTB Culture of CSF was negative,** India ink test – No Cryptococcus seen.

**MRI Brain plain and contrast** – multiple ring enhancing lesions, possibility of tuberculoma.

**MR SPECTROSCOPY BRAIN:** Lipid peak was observed, choline was high and N-acetyl Aspartate and creatine were low.

**MRI SPINE** – Suggestive of radiculomyelitis.

**BIOPSY** advised but patient was not willing. Patient was again started on a course of steroids (T.Prednisolone 60mg/d), and ATT (INH and Rifampicin) was continued. He showed clinical improvement after 10 days.

**Final diagnosis:** Ú A case of TB Meningoencephalitis Seizures secondary to Tuberculoma

**Paradoxical reaction to ATT presenting as:** -Multiple ring enhancing lesions -Spinal radiculomyelitis\[10\]

Patient was discharged with advice of continuing ATT, Steroids, Bladder training and regular follow-up.

Patient was under regular follow up, and showed significant clinical improvement after 8 weeks of steroids. A repeat MRI showed no new lesions, with disappearance of perilesional edema and a decrease in size of the older lesions and he was advised to continue ATT for 18 months

**DISCUSSION:**

Paradoxical reactions to ATT are defined as recurrence /new appearance of fresh symptoms, physical or radiological signs in a patient who had previously shown improvement with appropriate ATT.\[5\],\[6\] These reactions are very rare in HIV negative individuals: 2 -5% of HIV –negative patients, 7-10% of HIV –positive patients, 36% of HIV positive patients on ART. Paradoxical reactions are of two types: -Early reactions – occur <3 months of ATT. -Late reactions- occur may occur up to 18 months of ATT.

Paradoxical reactions to ATT have to be distinguished from ART associated TB- IRIS\[5\] where the patient, who is on ART and not ATT, develops IRIS due to recognition of TB antigens which are due to a new infection or a latent infection.

**CRITERIA FOR DIAGNOSING PARADOXICAL REACTIONS TO ATT: MAJOR:** -new or worsening CNS TB -new or worsening radiological features of TB -new or worsening serositis -new or
enlarged lymph nodes, cold abscess or other focal tissue involvement

MINOR: - new or worsening constitutional symptoms
- new or worsening respiratory symptoms
- new or worsening abdominal symptoms

These reactions do not indicate a failure or a resistance of the organism.\[7\],[8]\n
Paradoxical reactions are due to a complex interplay between the host's immune response and direct effect of mycobacterial antigens. Tuberculosis activates monocytes and increases interleukin levels and PG E2 levels leading to depression of type 4 hypersensitivity and immunosuppression. Once active TB is under control after starting ATT, immunosuppression resolves and leads to enhanced delayed type hypersensitivity. Activation and accumulation of lymphocytes and macrophages at the site of bacterial deposition or toxin production occurs when bacilli dies. In patients with paradoxical reaction to ATT, steroids are added or their dose enhanced and ATT is continued. The rationale behind use of adjuvant steroids lies in decreasing harmful effects of inflammation as the ATT kills the organism.\[9\]

REFERENCES:

1) Mohammad Wasay, Department of Medicine, the Aga Khan University, Karachi, Pakistan, J Assoc Physicians India 2003;51:257-260


5) Tuberculosis associated immune reconstitution syndromes [Indian J Tuberc 2010; 57:177-179]


