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Beyond Negative Microbiology: Disseminated Tuberculosis with Multiple Cerebral Tuberculomas in an Immunosuppressed Patient

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Abstract: ***Tuberculosis (TB) remains a major infectious disease burden in India, and extrapulmonary or disseminated forms may be microbiologically negative, especially in immunosuppressed hosts with paucibacillary disease. We report a 61-year-old man with rapidly progressive glomerulonephritis (RPGN) on cyclophosphamide who presented with acute right upper-limb weakness, generalised weakness, giddiness, fever and cough. MRI brain revealed multiple cerebral and cerebellar ring-enhancing and nodular lesions. Chest radiograph and HRCT chest demonstrated fibrocavitatory disease with centrilobular ground-glass nodules and tree-in-bud endobronchial spread, supporting active pulmonary tuberculosis. Despite negative sputum AFB smears, sputum/CSF MTB/, CSF cytology, India ink and Toxoplasma PCR, a clinico-radiological diagnosis of probable disseminated tuberculosis with multiple cerebral tuberculomas was made and empirical anti-tubercular therapy was commenced. The patient later developed sepsis-like deterioration and succumbed. The case highlights that, in TB-endemic settings, negative microbiology does not exclude CNS/disseminated TB in immunosuppressed patients, and that HRCT chest can be pivotal when CNS and sputum studies are non-contributory.***

Keywords: tuberculoma; multiple ring-enhancing lesions; CNS tuberculosis; disseminated tuberculosis; RPGN; cyclophosphamide; immunosuppression; smear-negative tuberculosis; endobronchial spread; empirical ATT

1. Introduction

Multiple ring-enhancing brain lesions have a broad differential: tuberculosis, pyogenic abscess, neurocysticercosis, toxoplasmosis, metastasis, glioblastoma, lymphoma, tumefactive demyelination, subacute infarct/haemorrhage, and vasculitic lesions. In a TB-endemic setting, tuberculoma remains a leading diagnosis, but confirmation is often difficult in immunosuppressed, paucibacillary disease.

Cyclophosphamide used for rapidly progressive glomerulonephritis impairs cellular and humoral immunity. It increases the probability of TB reactivation and dissemination while lowering sputum and CSF test yield. This case integrates the case report and HRCT imaging findings to emphasise modality-wise interpretation and missed diagnostic opportunities.

2. Case Presentation

A 61-year-old male, known hypertensive and a known case of RPGN on cyclophosphamide for one year, presented with right upper-limb weakness, generalised weakness, and giddiness for one day, with fever and cough for three days. Past surgical, family, personal history and habits were not significant.

He was well built and nourished, oriented to time, place and person, with GCS 15/15. Pallor was present in the detailed report, while icterus, cyanosis, clubbing, lymphadenopathy and oedema were absent. Vitals were normal. CNS showed reduced power in the right upper limb/hand; detailed notes recorded 0/5 power with hypotonia and diminished reflexes. RS showed reduced air entry on the right with crepitations. CVS and abdomen were normal.

Initial working diagnosis was acute CVA with right hemiparesis; he was referred for MRI brain stroke protocol. Imaging revised the problem to multiple intracranial ring/nodular lesions with probable tuberculomas in the clinical context.

Modality-Wise Imaging Findings

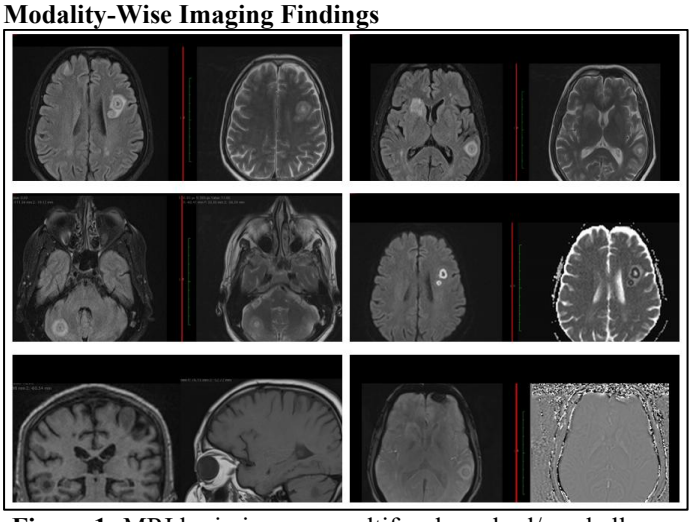

Figure 1: MRI brain images- multifocal cerebral/cerebellar ring and nodular lesions on FLAIR/T2/DWI/ADC/SWI/T1 images

MRI brain (plain): Multiple irregular ring-shaped and smaller solid nodular lesions were present in subcortical white matter, right caudate head, and right cerebellum; largest about 13 mm. Lesions showed central T2 hyperintensity with hypointense irregular wall, restricted diffusion of the wall, and minimal perilesional oedema. Ventricles/cisterns, basal

ganglia, brainstem, sellar region and major intracranial flow voids were preserved; Impression: multiple cerebral and cerebellar ring and smaller nodular lesions. CEMRI and MR spectroscopy were recommended but contrast MRI was not performed due to renal disorder and MR spectroscopy was not performed due to patient's financial constraints.

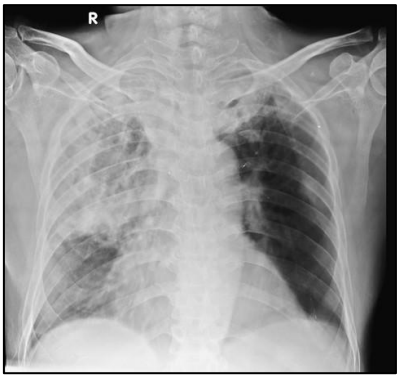

Figure 2: CXR from PPT - right upper/mid-zone inhomogeneous opacity with thick-walled cavity and fibrotic change; left upper-zone patchy opacity

Chest radiograph: Diffuse inhomogeneous opacity in the right hemithorax, predominantly upper and mid zones, with a thick-walled cavity in the right mid zone and additional lucencies suspicious for cavitation in right upper/mid zones. Fibrotic changes were noted in right upper/mid zones, with patchy opacities in the left upper zone. Cardiac size and CP angles were normal. Impression: multiple areas of cavitation and fibrosis in the right upper and middle zones with patchy consolidation in right upper, right middle and left upper zones.

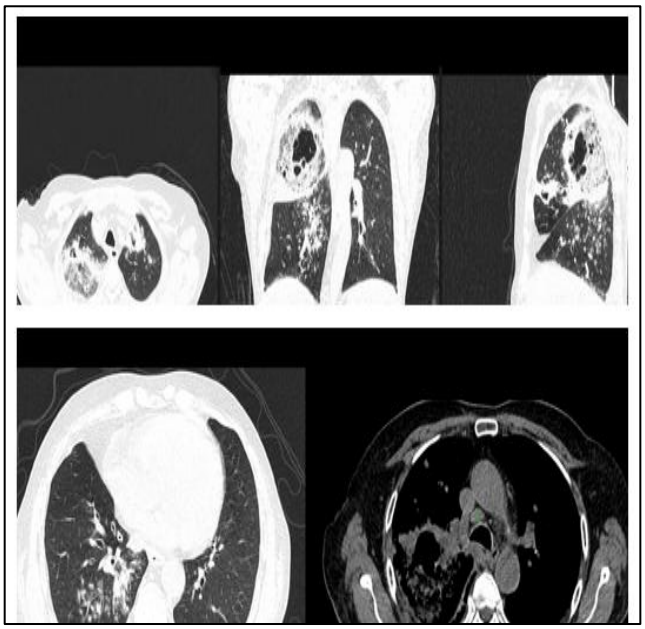

Figure 3: HRCT chest images- fibrocavitatory upper-lobe disease with centrilobular nodules/tree-in-bud endobronchial spread.

HRCT chest: Fibrocavitatory lesions with consolidation and centrilobular ground-glass nodules in a tree-in-bud configuration were present, predominantly involving right upper/middle lobes with left upper lobe involvement. Impression: pulmonary tuberculosis with active endobronchial spread. This was the pivotal investigation supporting disseminated TB when sputum and CSF tests were negative.

Abdominal ultrasound: Normal liver, gallbladder, pancreas and spleen. Both kidneys showed increased cortical echogenicity with preserved corticomedullary differentiation, no calculus and no hydronephrosis. Impression: bilateral medical renal disease; renal function correlation advised. Study was technically limited by reduced mobility.

Key Laboratory and Microbiology Data

- CBC: Hb 6.3 g/dL, RBC 2.25 million/cu.mm, TLC 5800/cu.mm, neutrophils 83.4%, lymphocytes 12%, platelets 1.31 lakh/cu.mm; ESR 156 mm/hr. Detailed report noted later Hb fall to 5.5 g/dL and post-PRBC Hb only 6.6 g/dL.
- Biochemistry: creatinine 2.1 mg/dL, urea 113.4 mg/dL initially, uric acid 10 mg/dL, albumin 2.4 g/dL; LFT largely normal. HIV 1/2, HBsAg and anti-HCV non-reactive, ESR-78
- CSF: clear/pale yellow, WBC 1 cell/uL, glucose 40 mg/dL, protein within reference range, ADA 0.10 U/L, LDH 24 U/L. CSF CBNAAT x2 MTB not detected; Gram stain/culture negative; India ink negative; Toxoplasma PCR not detectable; cytology negative.
- Respiratory: sputum AFB smear x2 negative and sputum CBNAAT MTB not detected.
- Urine routine showed numerous pus cells, bacteria 3+, trace protein and RBC 3-4/hpf, suggesting concurrent UTI/renal involvement context.

Differential Diagnosis

Most likely: probable disseminated tuberculosis with multiple cerebral tuberculomas, supported by TB-endemic setting, cyclophosphamide immunosuppression, very high ESR, MRI distribution, CXR cavitation/fibrosis, and HRCT tree-in-bud endobronchial spread. Negative AFB/CBNAAT/CSF tests do not exclude TB in immunosuppressed paucibacillary disease. Important alternatives: pyogenic abscess, neurocysticercosis, toxoplasmosis, metastases, glioblastoma/lymphoma, cryptococcosis, tumefactive demyelination, subacute infarct/haemorrhage, and ANCA-associated vasculitic CNS lesions.

Hospital Course and Outcome

The patient was managed in isolation. Given the CT chest findings and multifocal CNS lesions, empirical anti-tubercular therapy was started. Contrast MRI was not done due to renal impairment. Later, the patient developed worsening fever, sepsis-like deterioration and acute worsening sensorium, requiring MICU transfer. He subsequently suffered cardiopulmonary arrest; CPR was initiated according to ACLS protocol, and despite maximum efforts, the patient could not be revived.

Clinical cause of death documented in the detailed report: aspiration pneumonia; active pulmonary TB with endobronchial spread/disseminated TB; intracranial space-occupying lesion; severe anaemia of chronic illness. This remained a clinical diagnosis because there was no microbiological, histopathological or post-mortem confirmation.

3. Discussion

This case shows the diagnostic paradox of CNS/disseminated TB in a cyclophosphamide-treated patient: immunosuppression makes TB more likely but microbiological tests less likely to be positive. The HRCT pattern of fibrocavitatory disease with centrilobular nodules and tree-in-bud spread provided the strongest evidence for active TB and justified empirical ATT when no better alternative diagnosis was established.

However, the final diagnosis should be stated as probable disseminated TB with cerebral tuberculomas, not confirmed TB, because sputum and CSF studies were negative and no BAL, biopsy or autopsy was performed. In RPGN, ANCA-associated vasculitis can also cause CNS lesions and was not formally excluded.

Shortcomings:

- Bronchoscopy with BAL for AFB smear, CBNAAT, mycobacterial culture and fungal studies was the most important missed diagnostic step after HRCT showed endobronchial spread.
- Non-contrast MR spectroscopy could have helped: lipid-lactate peak supports tuberculoma; high choline/perfusion favours neoplasm.
- IGRA/QuantiFERON-TB Gold before and during immunosuppression was not documented; pre-cyclophosphamide TB screening is essential in TB-endemic regions.
- ANCA MPO/PR3 and anti-GBM antibodies were not documented despite RPGN; vasculitic CNS lesions therefore remained incompletely excluded.
- CSF cryptococcal antigen and fungal culture should be preferred over India ink alone in an immunosuppressed patient.
- Toxoplasma IgG/IgM serology was not sent; CSF PCR alone may be insensitive in immunocompromised patients.
- Severe anaemia needed reticulocyte count, iron studies, B12/folate, haemolysis screen, stool occult blood and possible bone marrow evaluation, but couldn't be done due to patient's financial constraints.

In India, tuberculosis must always be kept as the primary differential diagnosis for multiple ring-enhancing brain lesions, irrespective of smear, culture or CSF results.

Negative microbiology does not exclude TB, particularly in patients immunosuppressed by cyclophosphamide, steroids or biologics.

CT chest showing fibrocavitatory disease and a tree-in-bud pattern in a patient with multiple ring-enhancing lesions should be treated as near-conclusive evidence of disseminated TB, and empirical ATT should be started without delay when clinical probability is high.
Screen for those patients with a strong clinical suspicious for my form of TB/latent TB with IGRA before initiating immunosuppressive therapy. When TB is strongly suspected clinically and radiologically, treat and do not wait for microbiological confirmation. Delayed diagnosis and inadequate treatment of CNS TB in an immunosuppressed patient can be rapidly and irreversibly fatal.

Take Home Message
Even today, tuberculosis (TB), particularly disseminated TB, remains one of the greatest life-threatening infectious diseases. Hence, early diagnosis is the cornerstone of management and the key to preventing mortality. CT chest is often the pivotal investigation when sputum and CSF microbiology are negative in suspected disseminated TB. In TB-endemic regions, negative microbiological tests should never exclude TB when clinical and radiological suspicion is high. Pre-immunosuppression IGRA screening, early bronchoscopy with BAL when CT demonstrates endobronchial spread, and maintaining a high index of clinical suspicion are essential to facilitate timely diagnosis and prompt initiation of empirical anti-tubercular therapy, thereby improving outcomes and preventing fatal delays in treatment.

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