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Tuberculomas of central nervous system: A case series and review of literature

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Abstract
Background: Central nervous system (CNS) tuberculosis (TB) is rare complication of systemic tuberculosis. It can lead to abscess, tuberculoma, meningitis, or other manifestations. Sometimes it is difficult to diagnosis intracranial tuberculosis as clinical and imaging features resemble various other diseases, even malignancy. Most of these cases are found in immunocompromised patients. Antituberculosis therapy is the treatment of choice which significantly reduces the mortality.
Case series: Here, we are reporting a case series of CNS TB manifesting as tuberculoma in immunocompetent patients. All the patients showed clinical improvement after treatment with a combination of antituberculosis drug and corticosteroid.
Conclusion: Central nervous system tuberculoma in immunocompetent patient is a rare CNS TB manifestation and its diagnosis remain a challenge since its clinical symptoms and radiological findings could mimic other diseases such as pyogenic abscess, toxoplasmosis, neurocysticercosis, sarcoidosis, malignancy etc.

Keywords: mycobacterium tuberculosis, central nervous system, tuberculoma

1. Introduction
Mycobacterium tuberculosis infection may be manifested as pulmonary, extrapulmonary or both. Incidence of CNS TB is approximately 1% and 5–10% of all extrapulmonary tuberculosis [1]. Involvement of central nervous system is one of the most serious complication of tuberculosis infection. CNS TB involvement comprises of tuberculous meningitis (TBM), tuberculous encephalopathy, tuberculous vasculopathy, CNS tuberculoma (single or multiple), tuberculous brain abscess, (spinal) Pott's spine and Pott's paraplegia non-osseous spinal tuberculoma and spinal meningitis [2].
Young age, malnutrition, alcoholism, immunosuppression, HIV, malignancies, history of contact with open TB case, overcrowding etc are risk factors for tuberculosis [3]. In developing countries 1% of CNS TB presents as intracranial tuberculoma, which may be solitary or multiple (15-33%). Patients presents with signs of raised intracranial pressure such as vomiting, headache, seizure, hemiplegia [4]. Generally, children have infra-tentorial involvement and adults have frontal or parietal lobe involvement. In imaging studies initially may show low-dense or iso-dense lesions, while in later stage shows encapsulated hypodense or iso-dense lesions with peripheral ring enhancement (target lesions) [4]. Patients with HIV infection, lesions are more likely to be hypo- intense initially and later can be hyper-intense which may due to immunosuppression so there is delay in caseous necrosis of the capsule. Computed tomography (CT) scan is also done for monitoring the response to ATT and assessing the progression of disease [5].
Antituberculosis treatment of CNS TB is a four-drug regimen including rifampicin, isoniazid, pyrazinamide, and ethambutol (RIPE) or rifampicin, isoniazid, pyrazinamide with either fluoroquinolone or aminoglycoside, administered daily for two months. These four drugs (RIPE) are given for first 2 months and then followed by isoniazid and rifampicin for the rest of the course of 18 months. Ethambutol has poor CNS penetration which can be enhanced with use of fluoroquinolones. Steroids are usually combined for the first 2 months [6].

As clinical feature and imaging findings of CNS tuberculoma are nonspecific and thus it is challenging to diagnose. CT scan has a specificity of 85.7% and sensitivity of 100% in detection of CNS tuberculoma [7]. Magnetic resonance imaging (MRI) of brain is the investigation of choice. Lumbar puncture for CSF analysis is usually avoided because of risk for raised intracranial pressure (ICP) and which may leads to brainstem herniation. Moreover, most of the time CSF findings are non-contributory. Biopsy and histopathological should be done for confirmation of the brain lesions. But it is not essential due to some associated risk [7]. ATT can be started on the basis of clinically and radiologically suspicious lesion for the successful treatment of central nervous tuberculomas and should not be delayed for histopathological confirmation. Hence, this requires high suspicion for CNS TB, even in immunocompetent patient.

2. Case series

In our case series we are presenting three cases of CNS tuberculomas in immunocompetent individuals without any co-morbidities.

All the three patient had varied presentation which are summarized in table -1

Table 1: All the three patient had varied presentation which are summarized

Case no.	Age/ sex	Presenting complaints	Systemic Examination	Past history of tb/ History of contact	Radiological finding (NCCT Head)	Bone marrow examination	Gross finding	Microscopy	Ziehl Neelsen stain for AFB
1.	56 yrs/ male	Generalized weaknessx 5day Headachex 3day Fever x 2days Urinary incontinence vomiting	Lower limb examination (ankle and knee reflex exaggerated) Rest of the examination were within normal limits	No	A well-defined hypodense lesion measuring 16X15mm with thick wall measuring 4.8mm with surrounding oedema noted in the right parietal lobe, another similar lesion measuring 31X25 mm noted in the right post parietal lobe causing mass effect in the form of mid line shift. A provisional diagnosis of multiple tuberculoma was made	Normal	multiple grey white soft tissues pieces measuring 2.5x1.5cm	Section showed brain parenchyma with foci of necrosis and mixed inflammatory exudate. Foci of granulomas with central necrosis, with epithelioid cells, few giants cell and sheet of macrophages	Negative
2	11 years /girls	Headache for five days, fever for 2 days and with 8 episodes of vomiting. History of wight loss, night sweats were present	Yes	Lower limb reflexes knee and ankle both were exaggerate. Rest of the examination were within normal limits	A well-defined hypodense lesion measuring 46X15mm with thick wall measuring 2.6mm with surrounding edema noted in the right cerebellum, A provisional diagnosis of tuberculoma was made	normal	multiple grey brown soft tissues pieces altogether measuring 6x2x1cm	Section examined showed cerebellar area along with lesion. The lesion showed abundant area of caseous necrosis with well-formed epithelioid granuloma and giant cells and sheet of macrophages	Negative
Case 3.	46 years male	Generalised weakness for 11days, fever since 3 days. headache since 3 days and vomiting	Yes	Lower limb reflexes knee and ankle both were exaggerate. Rest of the examination were within normal limits	A well-defined hypodense lesion measuring 46X35mm with thick wall measuring 2.7mm with surrounding edema noted in the left thalamic region. With surrounding edema. A provisional diagnosis of solitary tuberculoma	Nil	Multiple grey brown soft tissues altogether measuring 4x3x0.5cm	Section examined showed extensive area of necrosis with surrounding area showing acute on chronic inflammation. Occasionally epithelioid cell granuloma also seen	positive

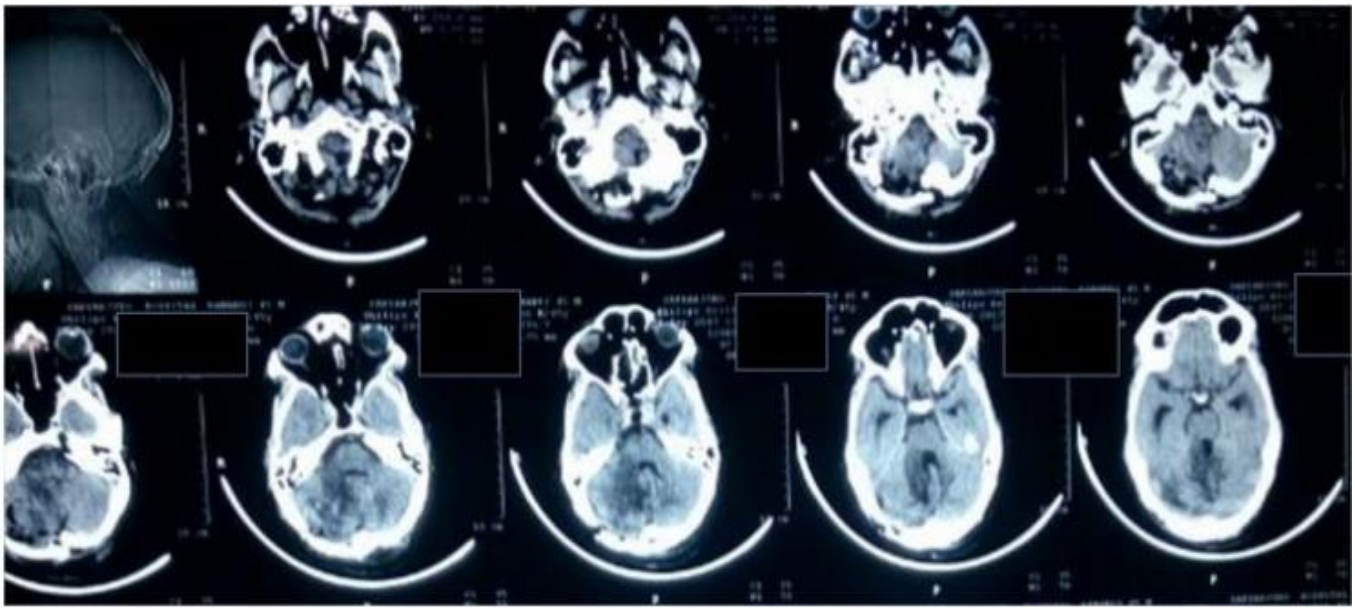

Fig 1: NCCT imaging showing cerebellar tuberculoma

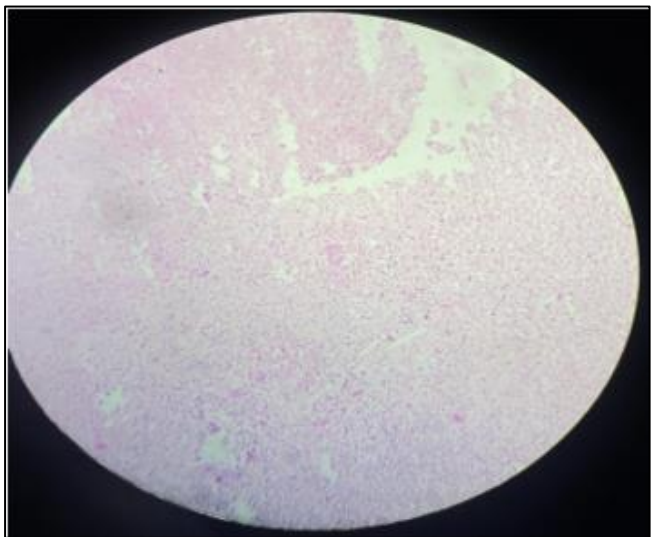

Fig 2: (10X)

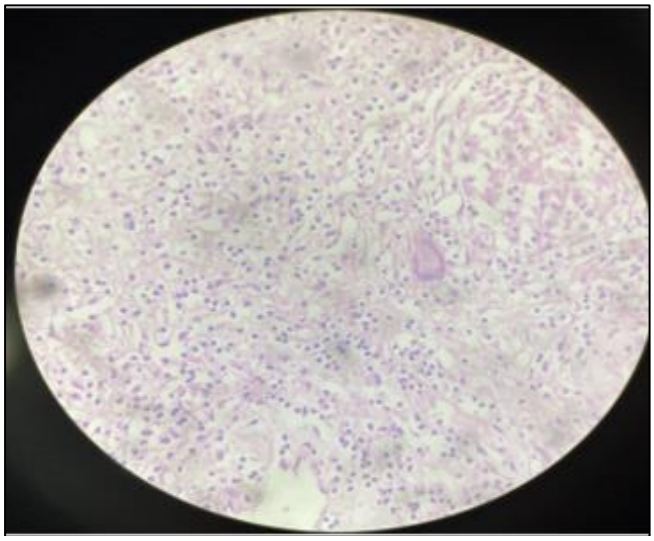

Fig 3: (40X)

Figure 2-3: Hand E stained section showing granulomatous inflammation, epithelioid Langhans giant cells, plasma cell, lymphocyte and areas of caseous necrosis.

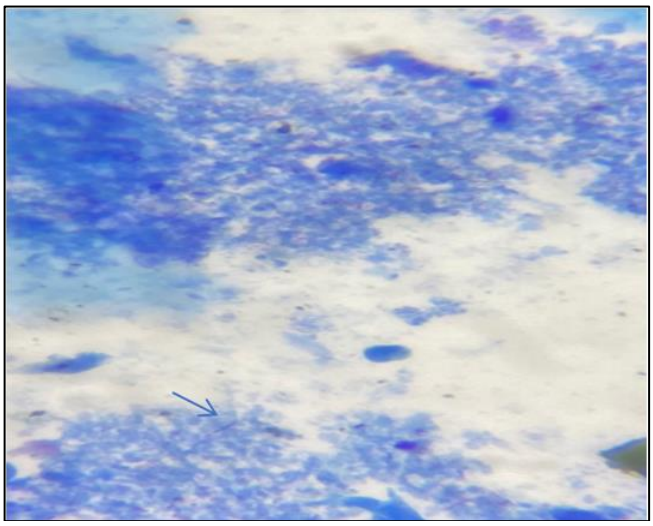

Fig 4: Zeihl Neelson stain for acid fast bacilli(100x)

3. Discussion

Tuberculosis is very common health problem in developing countries like India [8]. In approximately 1% cases tuberculosis get complicated with the involvement of CNS. Risk factors contributing are malnutrition, immunosuppression, alcoholism, extremes of age, malignancy [6, 7]. In our series no risk factors were except in one case where extreme of age was seen. Tuberculoma can presents as focal neurologic symptoms without clinical systemic manifestations. Imaging finding can mimic pyogenic abscess, neurocysticercosis, sarcoidosis or toxoplasmosis, malignancy etc [7, 9, 10] By the process of hematogenous spread from a primary focus such as the lung mycobacterium tuberculosis spreads to brain. When the cell-mediated immunity is low micro-organism inoculates in brain and tubercle focus on brain parenchyma can develop into abscess or tuberculoma [5]. In immunocompromised patients such as HIV intracranial tuberculoma is a rare complication and usually occur in tuberculosis patients and its incidence in patients without TB is not clearly known [11, 12].

Tuberculoma can occur in any organ of the body and infratentorial tuberculoma occurs commonly in children

whereas adults have more chances of supratentorial ones. Infratentorial tuberculoma risks patient's life more than supratentorial tuberculoma [13, 14]. The diagnosis, of the tuberculosis in these cases, made on the basis of was a positive result of CSF PCR for M. tuberculosis. Usually the microbial CSF culture for M. tuberculosis comes negative. Culture of mycobacterium is Gold standard for diagnosis. However, its sensitivity ranges from 25 to 70% only. Current diagnostic tests for TB have low sensitivity hence it difficult in early diagnosis of TB. Diagnosis of tuberculosis infection cannot be excluded from a negative microbial test [15]. PCR can detect M. tuberculosis easily but it can be positive in old treated tuberculosis cases [16]. In our study we did not do PCR and culture cause all the patients were presented with raised intracranial tension and got operated immediately.

After receiving category I antituberculosis drug treatment, the patients started to show improvement gradually (isoniazid, rifampicin, ethambutol, pyrazinamide and streptomycin). The patient also received dexamethasone injection with a dose of 5 mg every 6 hours, which was tapered off weekly. First 2 months of intensive phase patient received at least 4 regimens (Isoniazid, Rifampicin, Ethambutol and Streptomycin or Pyrazinamide) followed by a maintenance phase with Isoniazid and Rifampicin for 7-10 months [17].

Now after 12 months of follow up all the patients showed improvement.

Unal *et al*. in their series of 22 adult cases found that fever in 79%, alternated consciousness in 60%, headache in 57% and nausea and vomiting in 53% of the cases [13]. Neurological symptoms included seizures neck stiffness and motor deficits. In 8 cases, tuberculomas and meningitis coexisted and in half of them tuberculomas presented later. 50% patients had complete recovery, 36% had permanent neurological sequelae, 14% died during the course of treatment. In our series patients were presented with fever, headache, vomiting. All cases diagnosed as CNS tuberculoma without meningitis. During the follow up of 12 months all patients had complete recovery.

Wasay *et al*. in their review of 404 patients who were diagnosed with CNS TB in South Asian country observed that 39% patients had intracranial tuberculomas and tuberculosis meningitis (TBM) coexisted [10]. One fourth of Tuberculomas were diagnosed with the signs of infarction. In their study they concluded that risk factor of poor outcome were extremes of age, severity of TBM, infarction and hydrocephalus. Venter *et al*. in a case report of 24-year-old immunocompetent male in his imaging finding showed numerous infratentorial and supratentorial ring-enhancing brain lesions surrounding area showed oedema [16]. Lumbar puncture and Pleural biopsy were done for confirmation. Patient was put on Anti-TB along with Dexamethasone. Follow up Brain imaging after a few weeks showed improvement. Merison *et al*. reported a case with 8-year-old boy presented with headaches, left eye esotropia and optic disc oedema,, intermittent fevers for 5 months. Mantoux test was positive [18]. MRI revealed multiple hypointense rounded lesions with rim enhancement and perilesional oedema. After 17th of anti-MTB therapy on repeat MRI, showed decrease in size and enhancement of the tuberculomas On retrospective study from 1995 to 2009 in Houston by Kelly *et al*. of 12 adults with intracranial tuberculomas presented with altered mental status, night sweats and fever. 66.6% patients were diagnosed on histopathology [14]. Rest of patients were diagnosed on the basis of radiologic findings, presence of MTB other than CNS and response to anti- MTB therapy. One year mortality rate was seen in 16.7% patients and 20% overall morbidity rate. Sahaiu-Srivastava *et al*. reported a case of 32-year-old immunocompetent woman in California with clinical presentation of diplopia and Sudden-onset hemiparesis [15]. MRI brain showed enhancing lesion in the midbrain and thalamus and chest X-ray showed milliary MTB. Bronchoscopy sample was positive for MTB.

After completion of ATT, follow-up MRI showed complete resolution of the lesion. In another retrospective case series of 23 cases of CNS tuberculoma done by Bayindir C *et al* between 1988 to 2003 [12]. They found patients most commonly presented with headache, weight loss, weakness and fever, on imaging contrast-enhancing lesions were found in all patients and mostly located in supratentorial. Surgical excision of lesion was done in 21 patients and stereotactic biopsy was done in rest of cases. In majority of patients clinical symptoms were resolved after 3 months.

However, here we reported three cases of CNS tuberculoma in immunocompetent patients who had no previous history of pulmonary or extrapulmonary TB, but history of contact was seen in two patients. One case was confirmed by Ziehl Neelsen stain for AFB, rest 2 cases had granulomatous lesions histologically but AFB was negative. But they were diagnosed on the basis of imaging and responded well to ATT. Their symptoms improved after initiation of therapy.

In this literature review, CNS tuberculoma were diagnosed mainly on basis of clinical findings and brain imaging.

Multiple variables can affect the response of the disease to anti tubercular therapy. Both the sensitivity of the MTB strain to all drugs of choice as well as patient's medication tolerance are critical issues. Therefore, it has been suggested that treatment duration should be based on radiological response [19]. Continuing the treatment until total resolution of the lesions is probably prudent [19].

4. Conclusion

In conclusion, CNS tuberculoma is a rare CNS TB manifestation and its diagnosis remain a challenge since its clinical symptoms and radiological findings could mimic other cases such as malignancy, pyogenic abscess, toxoplasmosis, sarcoidosis, or neurocysticercosis. Antituberculosis drug medication is important to forestall complications and mortality and should be highlighted since it needs plenty of drug combination and long treatment length to realize a favourable outcome of the patients.

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