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**CASE REPORT**

# CNS TUBERCULOMA WITH PARADOXICAL RESPONSE AND TREATMENT CHALLENGE: A CASE REPORT AND LITERATURE REVIEW

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## ABSTRACT

*Central Nervous System (CNS) Tuberculoma, the most dangerous form of tuberculosis, remains a public health problem in developing countries. CNS tuberculoma, either single or multiple, usually presents as a diagnostic challenge because it resembles many other infectious and non-infectious medical conditions, particularly in patients without evidence of tuberculosis elsewhere in the body. There is no consensus regarding duration of antituberculous treatment, surgical indications and follow up management of these patients. Here, we report a case of confirmed CNS Tuberculoma in a 56 year-old man, who had persistent lesion after one year of chemotherapy with antituberculosis drugs and had therefore to finally undergo surgical intervention.*

***Key word:*** *CNS, Tuberculoma, Treatment*

## INTRODUCTION

Tuberculosis of the central nervous system (CNS) is a highly devastating form of tuberculosis, which, even in the setting of appropriate antitubercular therapy, leads to unacceptable levels of morbidity and mortality (1). CNS involvement represents almost 1% of all cases of active TB (2). Meningitis is by far the most frequent manifestation of tuberculosis in the central nervous system (3). However, intracranial masses remain an unusual presentation of such infection that usually affects immunocompromised patients. Central Nervous System Tuberculoma (CNST), either multiple or single, usually presents as a diagnostic challenge because it has a similar appearance to many other noninfectious and infectious medical conditions, specifically in patients without constitutional symptoms or evidence of tuberculosis elsewhere in the body (3).

Tuberculomas are granulomatous mass lesions composed of a central zone of caseation surrounded by collagenous tissue capsule arising in the brain parenchyma or the spinal cord (3-6). Diagnosis is established by CT/MRI with or without subsequent biopsy. Medical treatment is preferable to surgery and is the main stay of management unless there is a clear indication for surgical intervention (7,8). Controversies regarding treatment related issues such as paradoxical response during treatment, indications for surgical interventions and role of steroid are yet to be settled.

## CASE REPORT

A 58 year old, non-smoker, teacher, initially presented with progressive right sided body weakness. He had associated global headache and high grade intermittent fever preceding onset of weakness. He also developed generalized tonic clonic seizure which had repeated episodes. For this, he was evaluated at Ayder Referral Hospital. Imaging (Fig 1), CT -Scan of the brain showed ring enhancing (3.5 x 2 x 2.5cm) lesion on the left frontal region with marked perilesional edema and ipsilateral ventricular compression. With a consideration of brain abscess he was initiated on intravenous (IV) antibiotics, anticonvulsant and dexamethasone. Despite the above measures, patient was not responding; weakness and seizure persisted and patient's level of consciousness deteriorated. Imaging was repeated at this point (Fig 2) and showed a worsening picture with significant increment in size of mass and edema (Fig 2). With this, the patient was referred to Tikur Anbesa Specialized hospital. With the continuation of steroid and anticonvulsant treatment, the level of consciousness improved and seizure was controlled but other symptoms persisted.

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The patient did not have cough. There was no preceding history of trauma. No other pertinent history was identified. Upon evaluation at our hospital, he was chronically sick looking but his vital signs were stable with BP-120/80 and temperature of $36.8^0$C. He was conscious and oriented to person, place and time. Neurologic examination revealed right-sided hemiplegia with power of upper extremity 2/5 and lower extremity 3/5. Other parts of the examination were non remarkable and all meningeal signs were negative. Initial lab investigations showed a normal lab panel except for mildly elevated ESR (40 mm/hr). Additional imaging was also done (Figure 3). Treating Physicians considered tuberculoma as a top differential diagnosis followed by brain tumors (glioma) which could not be completely excluded. With these investigations, after case was discussed, patient was started on antituberculous drugs plus steroid and was appointed for follow up. After one year of therapy with first line anti-TB drugs (RHZE for two month and RH for 10 month) with good adherence and regular follow up at the neurosurgical referral clinic, the patient showed clinical improvement; headache subsided and weakness of extremities improved.

On subsequent follow up, one year and six month after initiation of anti-TB/six month after completion of anti-TB medication, patient had recurrence of headache and started to experience subtle weakness of right extremities and imaging was repeated (Fig 4) which showed no significant radiologic change compared with previous scan.

In short of diagnostic modalities (tissue biopsy) to rule out brain tumors and the assumption that after taking the drug for one year the patient would have been likely to respond to the anti-TB treatment, the case was reevaluated again and it was decided to opt for surgical intervention.

After one year and six months from his initial presentation the patient underwent a successful surgical intervention with full excision of the mass and the tissue was subjected to histopathology (Fig 5). Post-surgery, the patient's symptoms subsided, he regained full strength of the right extremities and his headache disappeared. One month after surgery patient was stable and discharged to be followed at both medical and neurosurgical side.

On the subsequent parts of this case report we will try to discuss practical points in relation to management of CNS tuberculosis with literature review basing our discussion on the above case.

In doing so, our main objective is to discuss the parameters used for follow up of patients diagnosed to have CNS tuberculoma, less common clinical presentations and scenarios encountered during follow up and to briefly see the controversial issues regarding management options.

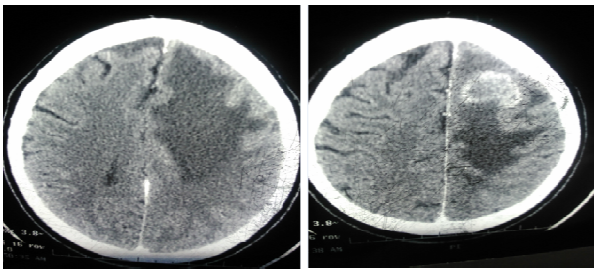

Fig 1:-Initial CT scan at presentation, showing ring enhancing lesion at the frontotemporal area with significant perilesional edema

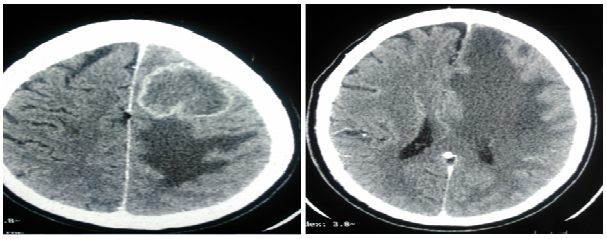

Fig 2:-CT scan taken after course of antibiotic showing worsening of perilesional edema with significant mass effect and ring enhancing lesion

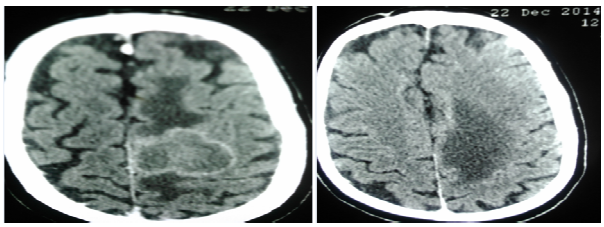

Fig 3:-CT Scan up on referral, showing similar findings with the above image but with decreased perilesional edema

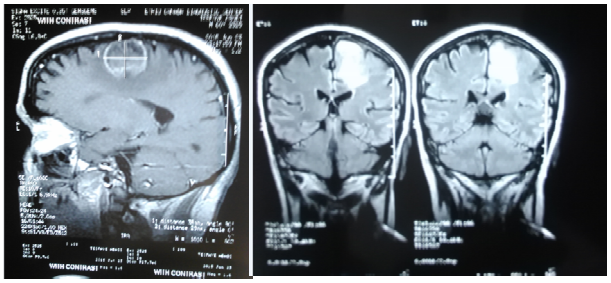

Fig 4: MRI with contrast taken after one year of anti-tuberculosis treatment showing no radiologic improvement.

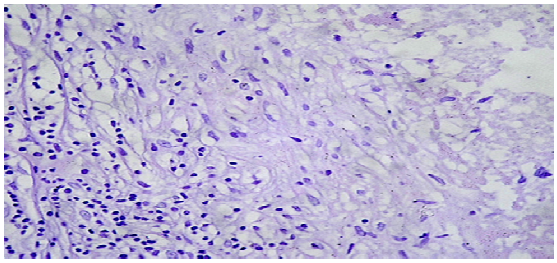

Fig 5: H&E stain of brain tissue showing a typical picture of caseous necrosis with epitheloid cells.

## DISCUSSION

CNS tuberculoma appears as a mass of granulation tissue made up of a conglomeration of microscopic tubercles. It results from the hematogenous dissemination of *Mycobacterium tuberculosis* from primary pulmonary infections and formation of small subpial and subependymal foci (Rich foci) in the brain and spinal cord (8). It accounts for 1% of all the disease caused by *Mycobacterium tuberculosis* but it comprises of 10-15% of extra pulmonary tuberculosis. It is mainly seen in younger patients with 60-70% of cases occurring in patients < 20 years of age and 20-30% of space occupying lesions in the brain in the developing world is attributed to CNS TB (8). It has been reported that the predominant locations of tuberculomas are supratentorial in adults and infratentorial in children (9). These are usually areas located in the corticomedullary junction and periventricular regions as expected for hematogenous dissemination (7). Brain stem tuberculomas are reported to be uncommon (2.5-8%). Most lesions measure >2cm but the size of tuberculomas may vary from 1-6 cm. Commonly, these are seen as solitary but multiple lesions are infrequent (9). The main challenge in the management of tuberculoma is its diagnosis. Its clinical features are varied and nonspecific ranging in severity from subtle to severe illness, partly depending on time of presentation. Imaging modalities enhance diagnostic certainty (10).

It is generally recognized that MRI is superior to CT in visualizing the morphological details of tuberculoma and particularly the tiny brain stem lesions. Enhancing lesions such as gliomas, metastatic tumors, abscesses, cysticercosis, mycotic and other granulomas can mimic the radiological features of tuberculomas(8). However, further improvements in diagnostic efficacy have been made possible by utilizing MR diffusion weighted imaging, spectroscopy and CT-guided biopsy (11).

Mainstay of treatment is initiating antituberculosis therapy with short course steroid upon indication. Surgical intervention has also a place in the management under the following scenarios: hydrocephalus, tuberculous abscess or if there is a need to relieve the mass effect acutely**.**

Isoniazid (INH) and Rifampicin (RIF) are key components of the regimen. INH penetrates the CSF freely and has potent bactericidal activity. RIF penetrates the CSF less well (maximum concentrations reach around 30% of plasma levels) but high mortality in case of RIF resistance in tuberculous meningitis has confirmed its role in treatment of CNS disease. There is no conclusive evidence to demonstrate that pyrazinamide improves outcome of CNS disease though it is well absorbed orally and achieves high concentrations in the CSF. There are no data from controlled trials to guide the choice of a fourth drug. Most authorities recommend either streptomycin (STM) or ethambutol (ETM), though neither penetrates the CSF well in the absence of inflammation and both can produce significant adverse reactions[8].

The question of the appropriate duration of treatment for CNS tuberculoma has remained unanswered because of the variable and uncertain influences arising from disease severity, CNS drug penetration, undetected drug resistance and patient compliance. Most authorities recommend 12 months of treatment. Different sources in the literature have shown that medical therapy can result in rapid and complete resolution of the lesion with clinical improvement (8).

Adjunctive steroid is recommended by different authorities though there are no published controlled trials which have examined whether patients with intracranial tuberculomas without meningitis or spinal cord tuberculosis benefit from adjuvant steroids. In general, different findings in the literature recommend initiation of steroids on the following clinical conditions: presence of significant perilesional edema, significant mass effect and in patients who have paradoxical progression under, or deterioration despite treatment (8).

For how long to treat tuberculoma is still a controversial issue. The rate of resolution of intracranial lesions on antituberculous therapy has been reported anecdotally in countries with high prevalence, and so far there is no consensus regarding the optimal duration of treatment (11). In general, the radiological response of tuberculomas can be assessed within 4-6 weeks while new or enlarging tuberculomas may occur in some patients despite adequate anti tubercu-

lous therapy (2). The activity of tuberculoma can generally be assessed by the degree of contrast enhancement on follow up CT/MRI. After 12 months of treatment, more than 2/3 of patients will still have contrast enhancing lesions. Though it is not clear if this represents an active lesion or just inflammation, continuing treatment is probably prudent. Total resolution of tuberculoma is observed when scans demonstrate no enhancing lesions or only an area of calcification. The literature recommends that treatment duration be tailored to radiologic response (7).

Paradoxically, tuberculomas can develop or enlarge during therapy leading to new neurological complaints, mainly of focal signs or with symptoms of increased intracranial pressure. A possible explanation could be the massive release of components of AFB (peptidoglycan and mucopeptide) soon after starting treatment which leads to inflammatory reaction[7]. This has been reported as early as two weeks and as late as 18 months of initiation of treatment. Addition of steroid, increasing the dose of drugs already in use or addition of second line antituberculous drug has been advocated to treat this phenomenon (12).

In our patient, recurrence of the symptoms after completing antituberculous therapy could be explained by immunologic reaction. The response after initial course of therapy excludes the possibility of drug resistance and suggests a paradoxical response. The absence of a clear worsening in the radiologic picture could be explained by early presentation of the patient following the development of the symptoms. In setups like ours, where resource is limited and further investigation of the patient to rule out other clinical conditions is not possible, one might consider surgical intervention as an option of treatment. However, we strongly believe that our patient could have been managed medically with continuation of antituberculous drugs, with the addition of steroid and surgical intervention could have been avoided.

In conclusion, considering the favorable outcome of medical treatment, especially among patients who present early and the high mortality associated with surgical intervention of such kinds of cases, we strongly favor timely initiation of medical therapy. All treatment should be based on the follow up of radiological resolutions and there should be a high index of suspicion for consideration of paradoxical response in those deteriorating after clinical improvement. Finally we strongly recommend that if there is a need, treatment can be prolonged beyond >12 months (2, 8, 11, 13).

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