Cerebral tubercular thrombophlebitis presenting as venous infarct: Magnetic resonance imaging and pathologic correlation

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Abstract

Central nervous system involvement by tuberculosis to produce basal meningitis, hydrocephalus, arteritis and infarcts is well-known, the brunt of the pathology being borne by the arterial vasculature to produce neurological sequelae. However, tuberculous thrombophlebitis causing venous infarction is exceedingly rare. We present imaging and pathological features of two autopsy proven cases of tuberculous thrombophlebitis with venous infarcts involving superficial venous system in one and deep venous system in the other. This is the first study presenting radiopathologic correlation of this rare complication. Tuberculous thrombophlebitis should be suspected if basal exudates and multiple white matter T2 hyperintensities are seen on neuroimaging and the imaging protocol should include both magnetic resonance arteriogram and venogram.

Key Words

Central nervous system tuberculosis, Magnetic resonance imaging, thrombophlebitis, venous infarct

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Introduction

The common mode of presentation of neurotuberculosis is tuberculous meningitis (TBM) followed by other pathological lesions such as tuberculoma, tuberculous abscess, meningoencephalitis with infarcts and tuberculous encephalopathy. Neurotuberculosis is almost always secondary to a primary lesion in the lung or other systemic organs, with the mycobacteria reaching the nervous system through hematogenous spread. A granulomatous and chronic inflammatory process that results in response to mycobacterial infection modulated by immunological status of the host produces a vascular pathology, most commonly affecting the arterial rather than venous system, thereby leading to ischemia and infarction. Based on the clinical features and imaging, Dalal *et al*.[1] from Western India and Thomas *et al*.[2] from North India reported that tuberculous vasculitis was responsible for ischemic stroke in young in 8% and 19% of cases respectively. On the other hand, among 193 autopsies of TBM not associated with human immunodeficiency virus (HIV) over a period of 20 years, a tertiary care center from South India reported ischemic arteritis and infarcts in 51 cases (26.4%).[3] Goldzieher and Lisa,[4] during the first half of 20th century documented gross cerebral hemorrhages and vascular lesions in cases of TBM and observed that hemorrhagic strokes were rare.

We present a detailed magnetic resonance imaging (MRI) and correlate with pathological features in two autopsy proven cases of chronic TBM with thrombophlebitis in immunocompetent individuals. To the best of our knowledge, no similar study has been reported in the literature.

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Case Reports

Case 1

A previously healthy 23-year-old man presented with fever, occasional headache and vomiting since 4 days, one episode of generalized tonic clonic seizures 2 days prior to admission to the hospital followed by altered sensorium and left sided weakness. At admission to the neurological services, he was

afebrile, not opening eyes to painful stimuli. Neurological examination revealed Glasgow Coma Scale (GCS) of 7/15, E1V2M4 with left hemiparesis. Both pupils were asymmetric and not reactive to light. The extraocular movements were restricted and ocular fundus revealed blurring of disc margins. Deep tendon reflexes were brisk and plantar response was extensor on the left and flexor on the right side. Routine hematological and biochemical parameters were normal. The serological tests for HIV, HBsAg, homocysteine, rheumatoid factor and antinuclear antibody were negative. Antemortem cerebrospinal fluid (CSF) analysis could not be done as lumbar puncture was clinically contraindicated. Electrocardiogram showed T wave depression in V1-V4 leads. Chest X-ray revealed inhomogeneous opacities in the left mid and lower zones with bilateral hilar prominence.

Cranial computed tomography (CT) scan highlighted hemorrhagic lesion in the right thalamus and right medial temporal lobe with multiple cerebral and cerebellar ring enhancing lesions. MRI brain [Figure 1a-e] revealed heterogeneous mixed signal intensity changes in the right thalamus, caudate, medial temporal region suggestive of hemorrhagic infarct with extensive perilesional edema extending into right internal and external capsules and corona radiata. The lesions bloomed on flash 2D sequences suggesting accumulation of paramagnetic substance, due to evolving hemorrhage. Lesions which were iso to hyper intense on T1WI and predominantly hypo intense on T2WI (T2 shortening) were noted in the right cerebral peduncle of midbrain suggestive of tuberculoma. Diffusion weighted imaging (DWI) revealed hyper intensity in the right thalamus, medial temporal and midbrain (facilitated diffusion) and hypo intensity in pons (restricted diffusion). Hemorrhage was extending into the lateral ventricle in both the occipital horns. The third and lateral ventricles were dilated with minimal periventricular hyper intensity suggestive of uncompensated hydrocephalus. Multiple rounded lesions iso intense on T1 and hypo intense on T2WI suggesting tuberculous granulomas were noted in the left side of pons, bilateral parasaggital basifrontal zones and left postero medial parietal lobe. There was diffuse sulcal hyper intensity on fluid-attenuated inversion recovery imaging (FLAIR) images suggestive of meningitis. MR venogram revealed non-visualization of the bilateral internal cerebral veins, vein of Rosenthal, vein of Galen and proximal segment of straight sinus and left transverse sinus (images are not available for documentation).

A diagnosis of pulmonary tuberculosis with multiple intracranial tuberculomata and thrombosis of cerebral deep venous system was made. Possibility of cerebral toxoplasmosis was also considered in view of multiple ring enhancing lesions. He received both antituberculous and antitoxoplasma chemotherapy with folinic acid for 5 days. He succumbed on the 6th day of admission to the hospital. Smear from the basal exudates of the brain revealed acid fast organisms by Ziehl-Neelsen stain. Serum and CSF samples collected at autopsy were negative for IgG/IgM antibody to *Mycobacterium tuberculosis*, *Toxoplasma gondii* and *Cysticercosis*.

Autopsy confined to the examination of the brain only was conducted 18 h postmortem with informed consent of close relatives. The brain weighed 1200 g and was edematous. Dural venous sinuses and superficial anastomotic veins were patent. The leptomeninges were hazy and had occasional tubercles in the parietal area along the course of the veins. The base of the brain had thick hemorrhagic exudate filling the chiasmatic, interpeduncular and pontine cisterns extending to foramen of Lushka, entrapping the cranial nerves and cerebral vessels. The internal carotid and vertebro basilar system were patent with no evidence of atherosclerosis. The crus cerebri on the right was necrotic and hemorrhagic dissecting down from the thalamus to midbrain and the medial temporal lobe on the right was softened. Bilateral cerebellar tonsilar herniation was noted, in spite of mega cisterna magna. On slicing the brain small tuberculomata were found in the left parietal cortex, pons and cerebellum corresponding to lesions on imaging. The right thalamic nucleus, internal capsule, putamen, hippocampus and right half of splenium of the corpus callosum showed hemorrhagic softening, rupturing into the third and lateral ventricle and extending down. The pons and medulla oblongata were enclosed in hemorrhagic inflammatory exudates. At the lower pontine tegmentum and along the foramina of Lushka on both sides, close to choroid plexus tiny tuberculomas were seen in the cerebellum. On the surface the pontine and cerebellar veins were found thrombosed and enclosed in the exudate [Figure 1f-i].

The histological examination of the representative neuroanatomical areas revealed multiple tuberculomas with caseous necrosis, perilesional edema and reactive astrocytosis. Small venous channels draining into the pontomesencephalic veins and the cerebellar veins were found thrombosed and enclosed in tuberculous inflammatory exudates. Similar to arteries, some of the small veins revealed granulomatous phlebitis. The topographic distribution of hemorrhage lesions

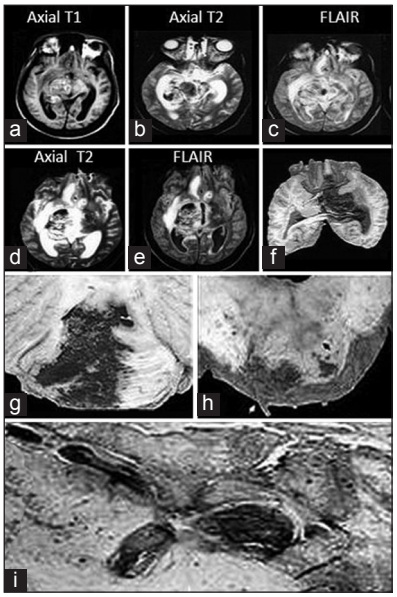

Figure 1: (a-c) Tuberculoma at the midbrain level iso and hypo intense on T1 and T2 respectively. (d and e) Hemorrhagic infarct at thalamus (right) and caudate nucleus. Axial section of the brain, (f) right thalamic hemorrhagic lesion extending from splenium through thalamus up to midbrain. (g) Right rostral pontine hemorrhagic lesion extending to the fourth ventricle. (h) Mid pontine level thrombosed vein (white arrow) and tuberculoma (right) (black arrow). (i) Microphotograph: Thromobosed veins and arteries entrapped in fibrin rich inflammatory exudate and extending into brain stem (H and E, ×Obj 2.5)

correspond to the venous drainage area of basal vein of Rosenthal, anterior and posterior mesencephalic veins. The transverse pontine veins, the retrotonsilar veins of the cerebellum and segment of internal cerebral veins and thalamo-striate veins bilaterally but asymmetrically revealed tuberculous thrombophlebitis along with arteritis of the small perforator vessels, thus highlighting the hemorrhagic lesions and masking the small arterial ischemic lesions. Though the tuberculomas indicate chronic pathology, the acute phlebitis suggests an acute exacerbation of an immune complex mediated granulomatous pathology (Theortical possibility of immune reconstitution secondary to ATT needs to be considered).

Case 2

A 30-year-old agricultural laborer presented to the neurology services with a history of three episodes of generalized tonic clonic seizures, irritability, bursts of anger, abusive behavior and inability to recognize close relatives spanning over a period of 1 year and fever with a head ache for 7 days. At 3 days after the onset of fever patient lapsed into altered sensorium along with urinary incontinence. On the day of admission to the hospital, the patient developed right sided weakness.

On examination, the patient was febrile, the rest of physical parameters and vitals being normal. Neurological examination revealed GCS of 6/15, E1V2M3 and right hemiparesis. The patient was not opening his eyes to deep painful stimuli and the extra ocular movements were restricted with papilledema. Both pupils were not reactive to light and dilated. The deep tendon reflexes were brisk with an extensor plantar response on the right side and flexor plantar on the left side.

Complete hemogram and peripheral smear examination were normal, but for a total leucocyte count of 15,200 and erythrocyte sedimentation rate of 65 mm/1 h (Westergren). The routine biochemical parameters were normal except for mildly elevated liver enzymes. Tests for HIV and HBs were negative. CSF analysis revealed a cell count of 170 cells (80% polymorphs), protein 117 mg% and sugar –11 mg%. Cranial CT scan revealed multiple disc enhancing lesions both in the cerebral grey and white matter and brain stem with edema and hydrocephalus.

MRI revealed [Figure 2a-e] multiple subcortical hyperintensities in the bilateral frontal, parietal, temporal white matter and in the pons and midbrain region on T2 and FLAIR images. A few well defined T2 hypointense lesions suggestive of small tuberculomas were also noted in the subcortical location in the bilateral frontal regions. Heterogeneous signal intensity was noted in the left thalamus and caudate nucleus. These lesions were iso to hyper on T1W1 and predominantly hypointense on T2 weighted images with perilesional edema. The lesions bloomed on gradient imaging suggesting a hemorrhagic component. The hyperintense lesions on T2 and FLAIR showed a mixed pattern of restricted and facilitated diffusion. DWI revealed hyper intensity in right frontal subcortical white matter showing restricted diffusion on apparent diffusion coefficient (ADC) maps. MRI brain revealed multiple discoid irregular enhancing lesions in the white matter extending into grey matter. FLAIR images revealed multiple serpegineous hypointense lesions in high parietal section showing thrombosed cortical veins as hypointense curvilinear structures.

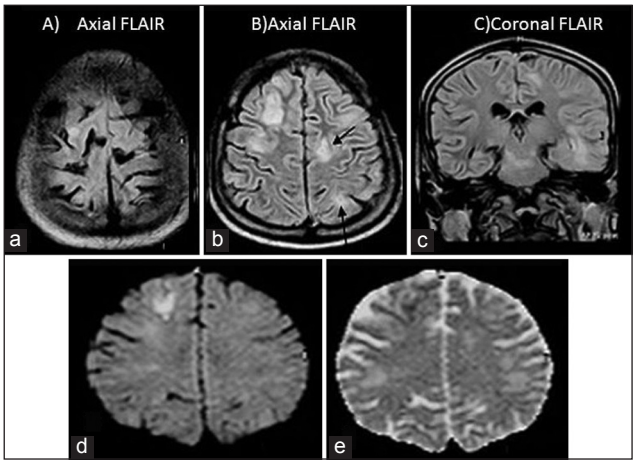

Figure 2: (a) Fluid-attenuated inversion recovery imaging (FLAIR) high parietal: Thrombosed cortical veins as hypointense linear structures. (b) FLAIR: Multiple subcortical hyperintensities. Few hypointense lesions in the bilateral frontal subcortical location (black arrow) probably tuberculomas. (c) Coronal FLAIR image showing hyper intensity in the bilateral temporal and left parietal subcortical white matter and in the pons. (d) Diffusion weighted imaging and (e) Apparent diffusion coefficient (ADC) map showing restricted diffusion in the right frontal sub cortical white matter. Note that not all the lesions which are hyperintense on diffusion weighted imaging are showing restricted diffusion on ADC

The patient received antitubercular drugs and steroids. Clinical diagnosis of TBM with multiple tuberculoma was made. Possibility of cerebral toxoplasmosis and cysticercosis were also considered in view of ring enhancing lesions and the endemicity. However he succumbed on 4th day of hospital admission. Autopsy confined to the examination of the brain alone was conducted 13 h after death following informed consent of the close relatives [Figure 3a-e]. Smear from the basal exudate revealed numerous acid fast organisms on Zeihl-Neelson stain. Post mortem serum and CSF were positive for mycobacterial antibody and IgG and IgM type mycobacterial immune complex and negative for cysticercosis and toxoplasmosis. Brain weighed 1200 g and appeared edematous and congested. The superior sagittal sinus along its entire length was thrombosed with extension into the left transverse and sigmoid sinus and involvement of proximal right transverse sinus, straight sinus and the vein of galen were patent. Several superficial cortical veins over the right posterior frontal and parietal lobes were thrombosed, the parenchyma underlying these vessels being softened and hemorrhagic.

The leptomeninges were hazy with creamy exudates and small tubercles along the course of the sylvian fissure and basal cisterns, obscuring the underlying structures. Coronal slicing of the brain revealed a large hemorrhagic lesion in the parasagittal right frontoparietal area involving the white matter with edema reflecting venous pathology. Left basal ganglia and thalamus had ischemic infarcts with zones of petechial hemorrhage, representing reperfusion. The brain stem and cerebellum were covered by thick exudates and in ventral mid brain (substantia Nigra) a tiny tuberculoma was found.

Histological examination revealed organizing thrombus in the venous sinuses and major superficial veins. Tiny tubercles were

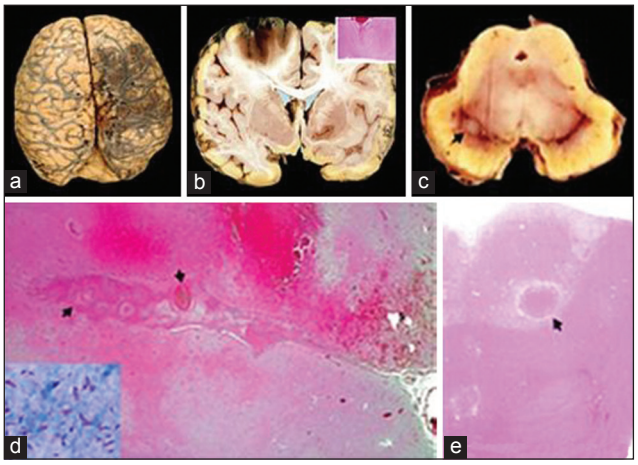

Figure 3: (a) Thrombosed superficial cortical veins with hemorrhagic infarct (right). (b) Coronal: Large left parietal cortical subcortical hemorrhagic infarct. Inset histology: Thrombosed veins in subarachnoid space (H and E, ×Obj 5). (c) Axial (mid brain superior colliculus) tuberculoma in substantia nigra (arrow). (d) Histology: Cerebral cortex showing dense exudate along the sulcus entrapping the vessels with adjacent hemorrhage (H and E, ×Obj 2.5). Inset-Exudate with acid fast mycobacteria (Ziehl-neelsen ×Obj 40). (e) A pontine tuberculoma (corresponding to coronal fluid-attenuated inversion recovery imaging (H and E, ×Obj 5)

observed in the frontal lobe along the walls of the superficial anastomotic veins. In the subarachnoid space the veins were entrapped in the chronic inflammatory exudates. Numerous Acid Fast Organisms were found in the exudates covering the vessels. The ventricular ependyma was normal. There was no granulomatous response or inflammation in the thrombosed dural venous sinuses.

Discussion

Tuberculosis is endemic in developing countries with the resurgence in the developed countries following the HIV acquired immune deficiency syndrome epidemic[5] and frequent migration of people across geographical zones. Central nervous system tuberculosis in spite of protean clinical manifestations and imaging features cause significant morbidity and mortality. Vascular complications associated with TBM are often secondary to arteritis and thrombosis resulting in ischemic lesions in the brain. The venous pathology following neuro tuberculosis is considered to be rare.[6]

In a preliminary analysis of 40 autopsied cases of TBM at Department of Neuropathology, NIMHANS venous infarcts in hypothalamic zone were noted in six cases, brain stem in 14 and brain stem with diencephalic involvement in 12 cases.[7] On histological evaluation, arteritis and venulitis were equal in frequency while venous thrombosis was less frequent especially involving large territories of venous drainage, where arterial and arteriolar pathology is more evident. Compared to the supratentorial compartment, in the infratentorial compartment a combination of arterial venous pathology secondary to tuberculous pathology appears to be more frequent.[7] In both cases in this study, the superficial anastomostic veins along the superolateral surface of the brain revealed granulomatous venulitis, but no luminal thrombosis. On the other hand the cerebral veins at the base of the brain especially those in the cisterna ambiens around the brainstem and cerebellum revealed thrombosis, extending into venous sinuses. These veins revealed granulomatous phlebitis in addition to organizing thrombosis. In addition, necrosis of the venular walls and hemorrhagic infarcts were observed in anatomical territories drained by deep venous system like in splenium of the corpus callosum, hippocampus, diencephalic nuclei, upper brain stem and cerebellum. The cases with venous infarct especially involving the deep venous system had acute clinical course with high mortality as noted in the present case. Poltera from Belgium in a 20 year post mortem study of TBM with intracranial vasculitis found phlebitis in 22 cases and thrombophlebitis with venous hemorrhagic infarct in 10 cases.[8]

Though literature has numerous account of CT and characteristics of tuberculous pathology there is no description of MRI characteristics of hemorrhagic venous infarct secondary to tuberculosis especially involving the deep venous system of the brain. In this study, the imaging characteristics of tuberculoma in the parietal cortex and pons were similar to those described in literature with heterogeneous signals, iso to hyper intense on T1WI and predominant hypontensity on T2WI. Blooming of lesions in posterior diencephalic nuclei and white fiber tracts on gradient imaging indicate seepage of paramagnetic substance from hemorrhagic regions and pooling in the territory of basal veins. Blocking of basal vein of Rosenthal, vein of Galen and initial segment of straight sinus could be visualized by MR venogram, the histology revealing phlebitis and venous thrombosis. In addition the perforating arterial branches entrapped in the tuberculous inflammatory exudates could have contributed to ischemic pathology enhancing the tissue morbidity, but masked by hemorrhage.

The cases with tuberculous phlebitis reveal areas of restricted as well as free diffusion. It is well-recognized that DWI/ADC pattern of venous stroke may be more heterogeneous than previously thought.[9] Large areas of reduced ADC values that are not predictive of ultimate infarction may be observed in patient with cortical venous thrombosis (CVT) reflecting accumulation of transudate with high protein content. These findings may have therapeutic and clinical implications.[9]

CVT is a well-known cause of hemorrhagic stroke with relatively obscure patho physiologic features that differ from arterial stroke. Break down of the blood brain barrier and coexistence of cytotoxic and vasogenic edema due to venous stasis are predominant pathogenetic events.[10] Granulomatous tuberculous arteritis and arteriolitis is the basal cisterns though is a chronic, slowly evolving pathology, the phlebitis with large zones of hemorrhage and edema could cause mass effect. This acute hemorrhagic lesion can lead to acute exacerbation of pathology and rapid progression of the disease with significant clinical morbidity. In cases of TBM or systemic tuberculosis with hemorrhagic lesion in the brain, venous infarct secondary to infective thrombophlebitis needs to be considered. MR venogram can assist in delineating the compromised venous territory with complete or partial block. These features help in mapping the affected venous territory in the damaged brain and plan appropriate therapeutic interventions to limit the morbidity. Whether these lesions of

venous thrombosis, stasis and hemorrhagic infarcts during the course of tuberculous pathology need to be managed like non-infective venous thrombosis with anticoagulant therapy needs to be evaluated.

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