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Clinicopathological Conference Report—PM 25381

Postpartum Prothrombotic State with Multiple Brain Infarcts Mimicking Tuberculous Meningitis with Vasculitis

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This case (PM 25381) was discussed on 22nd July 2013 as a student clinicopathological exercise at Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, India.

Clinical details and Case analysis: Dr Bikram Shah, Junior Resident, Department of Internal Medicine, Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, India

CLINICAL DETAILS

A 23 years old female presented on 29th April 2013, with complaints of fever of 3 months duration, seizures and altered sensorium for one week. Fever was low grade (up to 100º F), intermittent, and not associated with chills and rigors and subsided with medication. The patient had generalized tonic clonic seizures since 7 days and had nine episodes of seizures in 4 hours and altered sensorium since then. The altered sensorium was in the form of unresponsiveness to verbal commands, not recognizing relatives and was associated with uprolling of eyeballs and tongue-bite. The patient had a background history of single episode of seizure, three and half months back, 3 hours postpartum. The antenatal period was uneventful, and she delivered a live male baby. She was managed conservatively and discharged in the postpartum period. She had no history of headache, vomiting, blurring of vision, trauma, cough, shortness of breath, chest pain, jaundice, abdominal pain, joint pains, rashes and bleeding tendencies, loss of appetite or loss of weight. No other significant family history was obtained. On general physical examination, she presented with fever, hypotension (90/70 mm of Hg), tachycardia (170/minute and feeble) and respiratory distress (respiratory rate 40/minute and gasping) with Glasgow coma scale (GCS) of 3/15 (E1M1V1) and doll's eye reflex was absent. Systemic examination revealed signs of meningism in the form of neck-rigidity and Kernig's sign was positive, brain stem reflexes were absent, pupils were bilaterally small and sluggishly reacting. The muscle tone and bulk were normal, power could not be assessed, deep tendon reflexes were 2+ in bilateral upper and lower limbs. The bilateral plantar reflexes were mute. Rest of the systemic examination was within normal limit. Investigations revealed anemia (predominantly normocytic and normochromic with few microcytes), raised ESR (60 mm), transaminitis (SGOT-581/ul, SGPT-129/ul, alkaline phosphatase-279/ul), hypoalbuminemia (albumin 2.1 g/dl), and raised serum creatinine (2.19 mg/dl). The coagulogram showed prolonged PT (21 seconds; control 14 seconds), aPTT (39 seconds; control 32 seconds) and deranged prothrombin index (PTI) (66%) and International normalized ratio (INR) (1.44). However, the fibrinogen was normal and D-dimer was present. CSF analysis revealed increased cells, initially polymorphs (10 cells/ul) and later lymphocytic pleocytosis (70 cells/ul) with low sugar (29 mg/dl), high protein (152 mg/dl) and ADA of 20 U/L. Gram stain, cryptola and TB-PCR in cerebrospinal fluid (CSF) were all negative. Routine urine analysis revealed trace amount of albumin, no sugar, 3-5 pus cells/hpf and no Red blood cells (RBCs). Blood culture and endotracheal tube aspirate cultures were

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negative. The ANA was 3+ positive with speckled pattern in 1:40 dilution and the ANCA was negative. The HBsAg, HCV and HIV serology were all negative. Malaria kit test was negative. The contrast-enhanced magnetic resonance imaging (CEMRI) of brain revealed multiple acute infarcts in pons, midbrain, superior cerebellar peduncle and temporal lobe with meningeal enhancement. The electroencephalogram (EEG) was suggestive of diffuse encephalopathy. The compression ultrasonography of bilateral lower limbs did not reveal any evidence of deep vein thrombosis. On the basis of the history of fever of 3 months duration, seizures and altered sensorium and CSF examination having predominant lymphocytic cells, low sugar, high protein and high adenosine deaminase (ADA), a possibility of infectious meningoencephalitis most probably-tuberculosis was kept. Patient was started on antitubercular therapy (ATT) and steroids, suspecting the multiple acute infarcts were due to tuberculous vasculitis. There was no improvement in GCS of the patient. Patient developed hypotension during the hospital stay and a possibility of pulmonary thromboembolism was also kept. Patient had a cardiac arrest, cardiopulmonary resuscitation (CPR) along with resuscitative measures was done but patient could not be revived and she succumbed to death on 5th July, 2013.

CASE ANALYSIS

In the above clinical scenario, we have a 23 years female who was symptomatic for last 3 months. She had low grade intermittent fever for 3 months and seizures and altered sensorium for 1 week. She had suffered a single episode of seizure 3 hours postpartum which was managed conservatively and her antepartum and peripartum periods were uneventful. On general physical examination, she was febrile, GCS was 3/15(E1V1M1), and there was tachycardia (PR-170/min), tachypnea (RR-40/min), hypotension (90/70 mm Hg), pallor present and neck rigidity. Her brain stem reflexes were absent, pupils were bilaterally small and sluggishly reacting, muscle tone and bulk was normal, deep tendon reflexes were 2+ in bilateral upper and lower limbs and the bilateral plantar reflexes were mute. Rest of the systemic examination was within normal limit. Investigations revealed anemia, raised ESR, transaminitis, hypoalbuminemia, terminally raised serum creatinine, deranged coagulogram in the form of prolonged PT, aPTT, PTI and INR, CSF analysis revealed increased cells, initially polymorphs and later lymphocyte predominant with low sugar and high protein and high ADA of 20U/L. ANA serology was 3+ speckled positive. The CEMRI of brain revealed multiple acute infarcts in pons, midbrain, superior cerebellar peduncle and temporal lobe with meningeal enhancement and the EEG was suggestive of diffuse encephalopathy.

Considering the data base, the following differential diagnoses were considered: (1) infective meningoencephalitis, (2) inflammatory meningoencephalitis. Of the infective causes, tuberculous meningitis is considered before fungal, viral and pyogenic meningoencephalitis. Of the inflammatory causes, SLE and secondary antiphospholipid antibody syndrome were considered. The multiple acute infarcts were possibly due to vasculitis associated with tuberculosis or inflammatory meningoencephalitis, the anemia could be nutritional or anemia of chronic disease, the transaminitis could be (a) ischemic, (b) drug-induced ATT or (c) disease related in origin.

Tuberculous meningoencephalitis: In this index, case presence of intermittent low grade fever for 3 months, seizures and altered sensorium, anemia and raised ESR, lymphocytic pleocytosis, high protein, low sugar and raised ADA in CSF, multiple infarcts with meningeal enhancement in CEMRI favors tuberculous meningoencephalitis. However, absence of any lymphadenopathy, normal chest X-ray and negative CSF TBPCR are against this diagnosis. Transaminitis can occur due to granulomatous hepatitis or can be drug-induced. Seizures may frequently occur during tuberculous meningitis and may be the presenting symptoms of tuberculous meningitis even in the absence of evident intracerebral lesions on MRI.[1] Stroke can occur in 30% of cases with tuberculous meningitis and it can independently predict poor outcome.[2] An Indian study showed CSF ADA level 10 U/L as a cutoff value with 94.73% sensitivity and 90.47% specificity in differentiating tuberculous from non-tuberculous meningitis. So, considering all these findings a diagnosis of tuberculous meningitis is likely.

Fungal meningitis: The chronic course of the disease, high protein and low sugar in CSF and CSF cells <300/ul, all favor the possibility of fungal meningitis. However, the patient is not immunocompromised, and the HIV serology is also negative making this possibility less likely.

Pyogenic meningitis (partially treated): Despite the presence of the signs and symptoms of meningitis and the CSF findings (high protein and low sugar), the prolonged duration of the illness (3 months) and a relatively non-fulminant course in this time period makes this possibility less likely. Studies have shown that seizures occur frequently in adults with community-acquired bacterial meningitis.[3]

Viral meningoencephalitis: This possibility is less likely as the CSF picture is not consistent along with long duration and the CEMRI findings.

Inflammatory disorders: The occurrence of seizures and encephalopathy in a young female, presence of anemia, ANA positivity and acute infarcts possibly related to vasculitis, all support the diagnosis of an inflammatory condition like SLE or Behcet's syndrome. However, the absence of any rash,

arthralgia, serositis and multisystem involvement makes this possibility less likely.

So, the most likely clinical diagnosis in this patient is meningoencephalitis most likely tuberculous with acute multiple infarcts (? vasculitic), status epilepticus causing hypoxic ischemic encephalopathy, sepsis with AKI/transaminitis (MODS—multiorgan dysfunction syndrome). The cause of death is refractory shock and?? pulmonary thromboembolism.

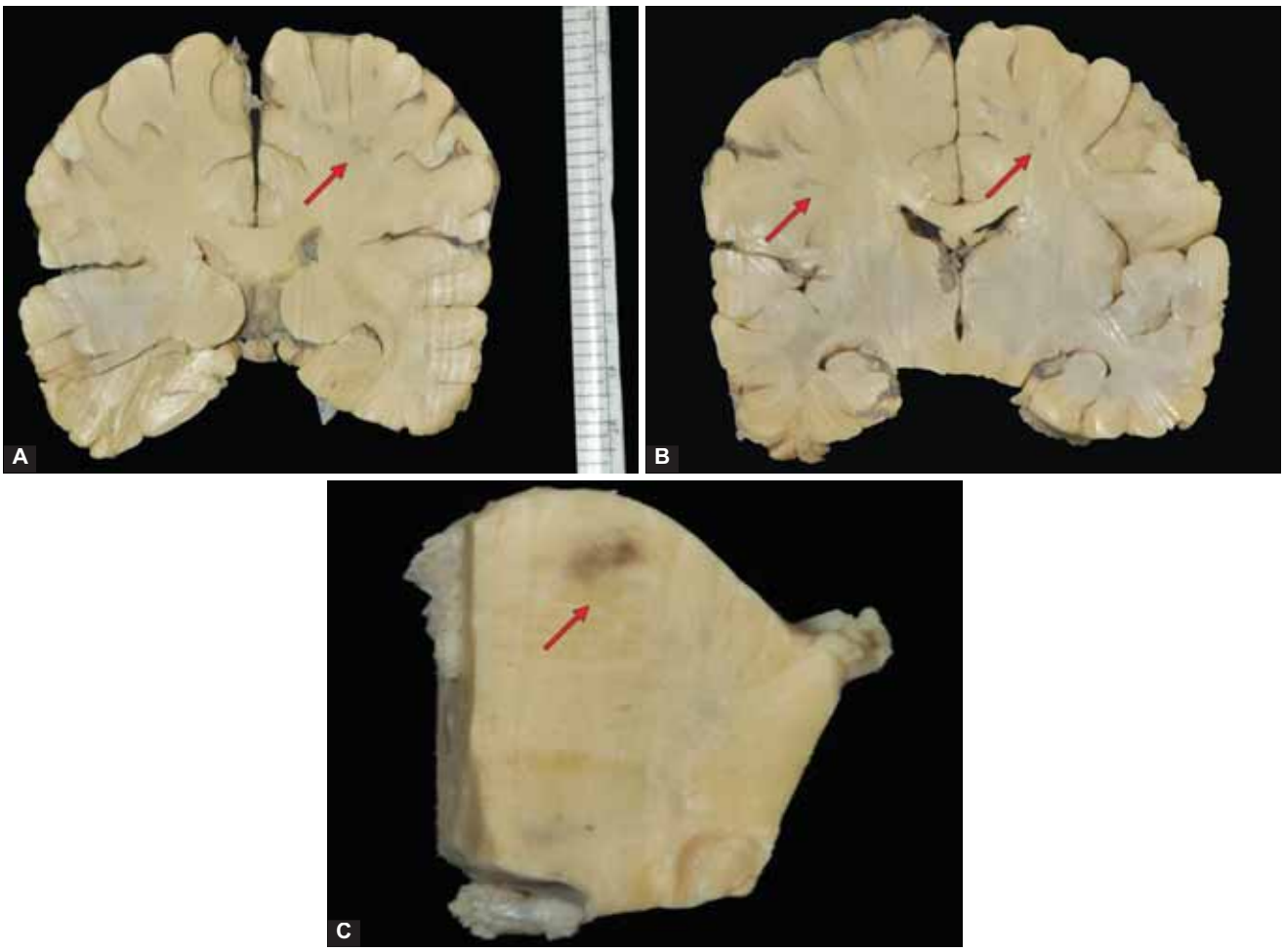
OPEN HOUSE DISCUSSION

Senior resident treating unit: The disease was undoubtedly chronic with the presence of anemia and hypoalbuminemia and many of the deranged biochemical parameters in this patient could possibly be contributed by the status epilepticus itself including the elevation of liver enzymes.

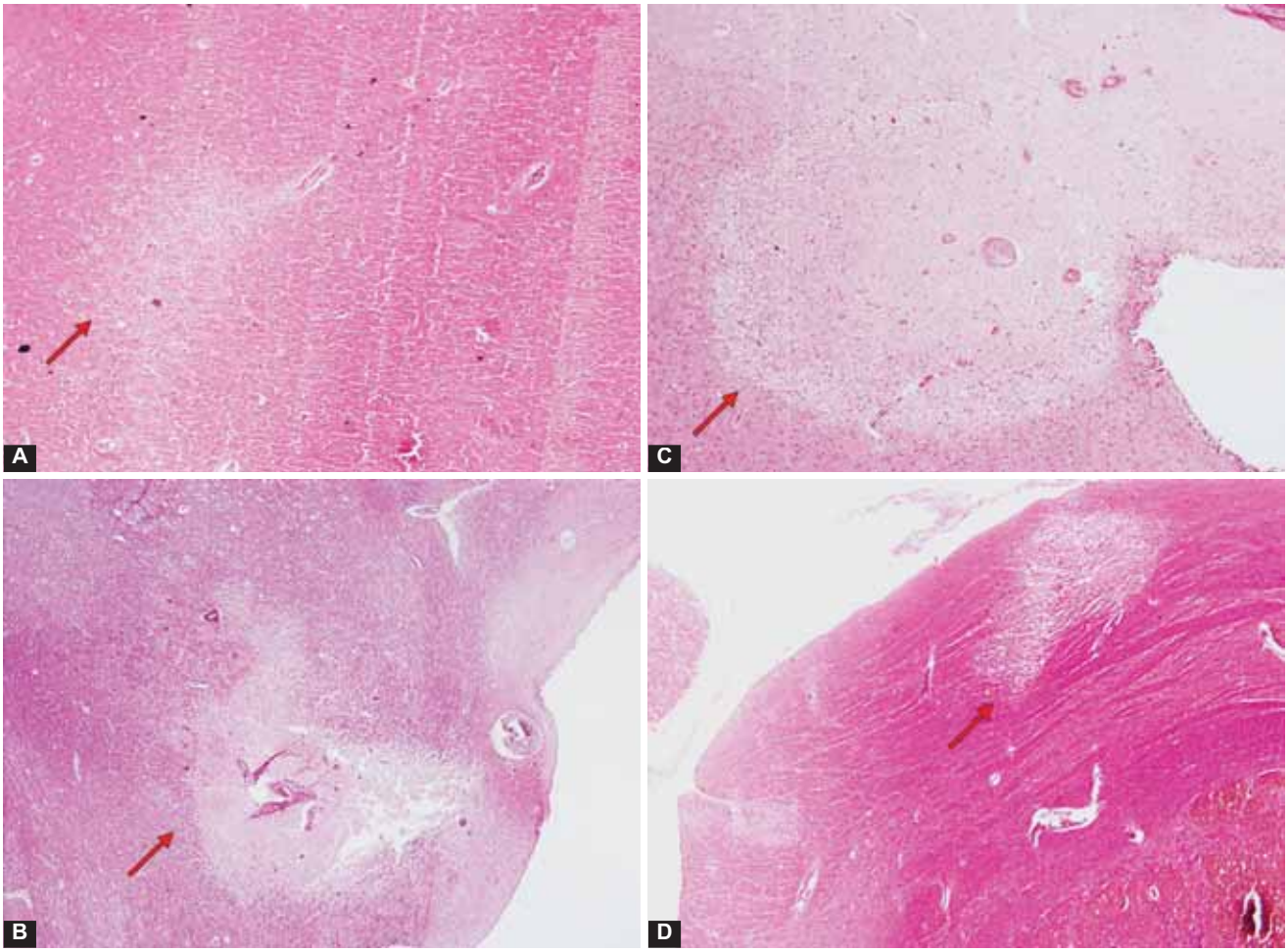
AUTOPSY PROTOCOL: PM 25381

(Dr Suvradeep Mitra, Junior Resident, Department of Pathology, PGIMER, Chandigarh)

A complete autopsy was performed in this 23-year-old female patient who was 4 months postpartum. The prosector noted that all the serous cavities were within normal limits. The brain weighed 1100 gm and showed mild meningeal dullness over the cerebral convexities. No basal exudates were identified and the basilar artery was unremarkable. No cortical venous thrombosis was noted. On coronal slicing, multiple discolored areas ranging in size from pinhead to 1.5 cm in diameter, in the central white matter, cerebral cortex, basal ganglia and brainstem (pons, floor of 4th ventricle, midbrain involving periaqueductal gray, cerebral peduncle and substantia nigra, superior cerebellar peduncle) were noted (Figs 1A to C). A cystic area measuring 1.5 × 1 cm was seen in the right inferior temporal lobe. Microscopically, all these areas showed multiple infarcts of different age and different size not pertaining to any arterial territory (Figs 2A to D). Immunostain for CD68 showed exuberant macrophage reaction around some of these infarcts proving them to be of some duration. These infarcts were dispersed in the deep parenchyma as well as near the surface. The surface infarcts elicited lymphohistiocytic meningeal reaction in their vicinity, probably explaining the lymphocytic pleocytosis in the CSF. Evidence of cortical ischemia in the form of nuclear pyknosis and cytoplasmic eosinophilia, axonal transection in the form of axonal bulb formation were also seen along with areas of ischemic demyelination. Fibrin thrombi were



Figs 1A to C: Gross photographs of infarcts in the brain parenchyma distributed widely (A and B) bilateral central white matter (C) base of the pons



Figs 2A to D: Microphotographs showing multiple infarcts in (A) basal ganglia, (B) floor of fourth ventricle, (C) periaqueductal gray and (D) basis pontis

seen in the small perforating vessels (Figs 3A and B). No granuloma was seen in any of these areas and the AFB stain was negative. The lungs weighed 980 gm. Grossly, the pleura was dull and the lungs were subcrepitant to feel and exuded frothy fluid on pressure. The second/third divisions of the pulmonary artery showed thrombi with small hemorrhagic areas dispersed in the subpleural zones of the lungs (Fig. 4A). Histopathological examination showed fibrin thrombi in the above branches of the pulmonary artery (Fig. 4B) with diffuse pulmonary edema and fresh intra-alveolar hemorrhage in the adjacent lung parenchyma. Terminal bronchopneumonia was also noted. No granuloma was noted anywhere in the lung parenchyma and no acid-fast bacillus was identified on AFB staining. The heart weighted 210 gm. Grossly, it showed mural and auricular thrombi. All four chambers of the heart and the inflow and outflow tracts were normal. There was no left ventricular or right ventricular hypertrophy or any atrial dilatation. Histopathological examination revealed mural thrombi and there were fibrin thrombi in the intramyocardial vessels as well (Fig. 4C). The liver weighed 2100 gm with grossly unremarkable capsular surface and cut surfaces. Hepatic veins and venous radicles contained thrombi with hemorrhagic necrosis of the adjacent area (Fig. 5A). No thrombus was seen in the portal vein. Microscopy revealed fibrin thrombi in hepatic veins (Fig. 5B) and smaller venous radicles with hemorrhagic necrosis of the adjacent hepatocytes, sinusoidal dilatation and congestion, hemosiderin deposition in the Kupffer cells and mild fatty change in the hepatocytes. However, there was no hepatocyte loss. The kidneys were normal grossly and showed normal glomeruli. No thrombi were identified in the glomerular vessels. No features suggestive of SLE were seen. Direct immunofluorescence for IgG, IgM, IgA, C1 and C3 were negative. Pigment cast was seen in the tubules, possibly as a result of episodes of intractable seizures and causing anuria. The bone marrow showed erythroid hyperplasia. The spleen weighed 190 gm and was enlarged with congested red pulp. Other organs, i.e. GIT, pancreas, adrenal and genital tract, were grossly and microscopically unremarkable.

Final Autopsy Diagnosis, 23-Year-Old Female Patient, 4 Months Postparturition

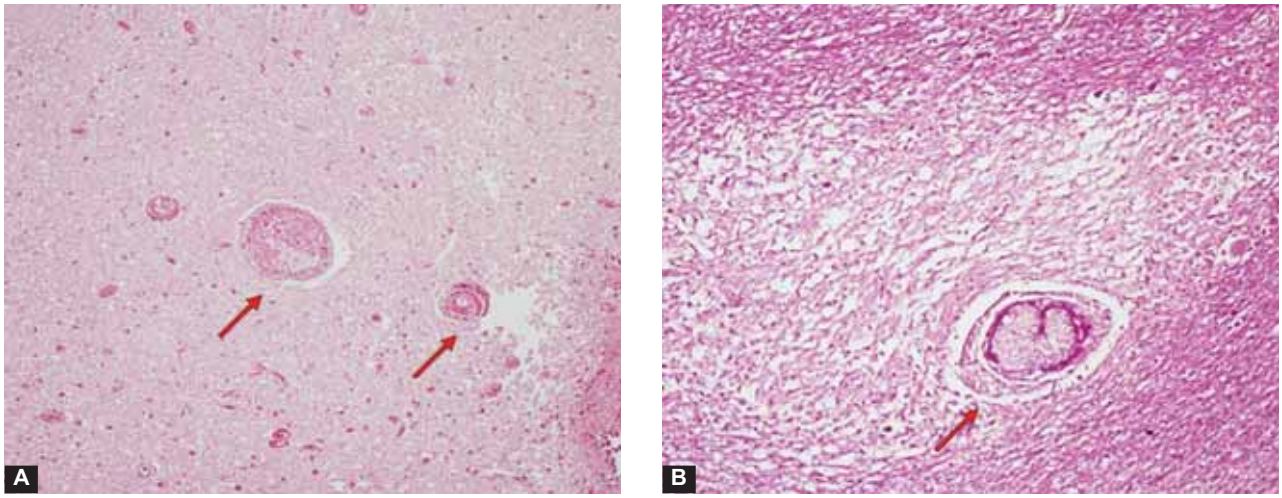
- Multifocal cerebral and brainstem infarcts due to thrombi in small perforating vessels

- Hepatic venous thrombosis and Budd-Chiari like features
- Intramural and intracardiac vessel thrombosis
- Pulmonary thromboembolism, pulmonary edema and terminal bronchopneumonia.

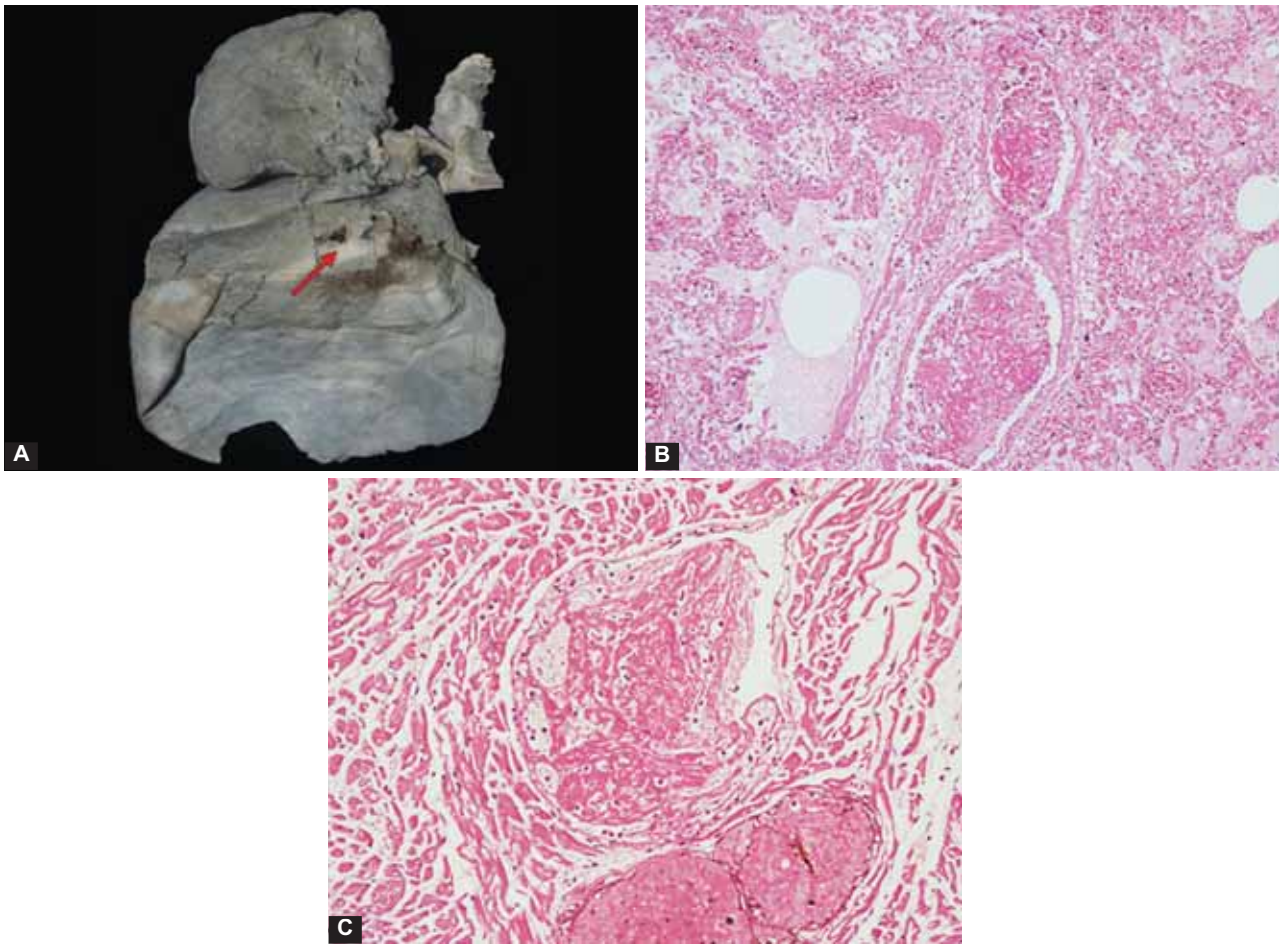
Possibly, related to a prothrombotic state? Protein C/S/ antithrombin deficiency, factor V leiden or a primary/ secondary APLA syndrome.

OPEN HOUSE DISCUSSION

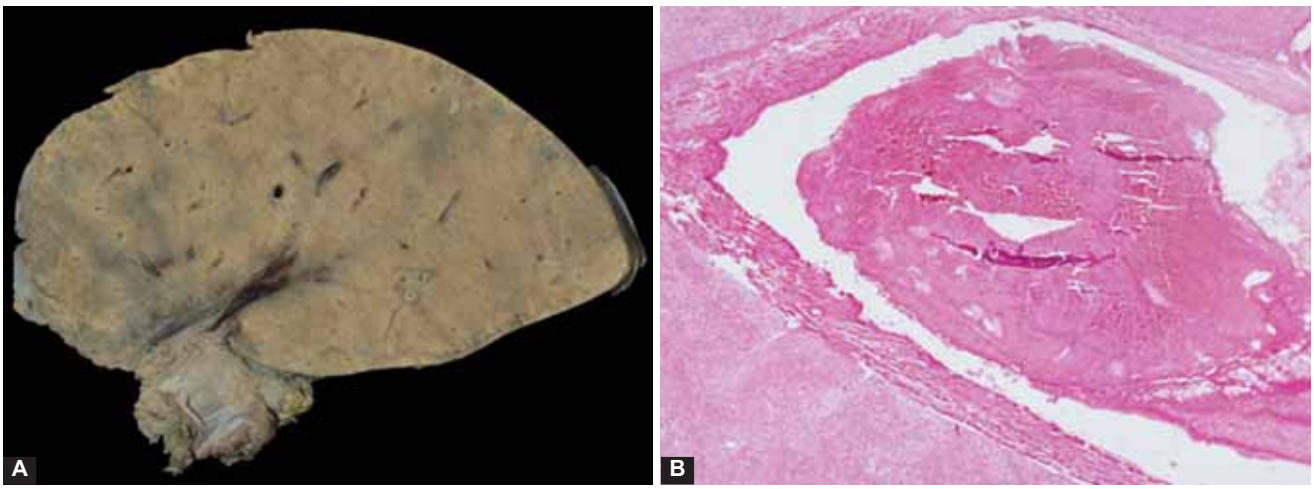
- *Prof S Varma:* Based on the data available, a diagnosis of lupus anticoagulant is difficult. This case exemplifies the fact that despite the presence of signs of meningitis, other possibilities should be kept in mind. The very early occurrence of seizure, late progression and low grade fever are the small oddities present in this patient.



Figs 3A and B: Microphotographs showing infarcts in different areas of deeper brain parenchyma with fibrin rich thrombi occluding the perforating vessels



Figs 4A to C: (A) Gross photograph of the lungs showing thrombi in the branches of the pulmonary artery, (B) microphotograph showing fibrin rich thrombi in the branches of pulmonary artery, (C) microphotograph of fibrin rich thrombi in the intramyocardial vessels



Figs 5A and B: (A) Gross picture of the liver showing thrombi in the larger hepatic veins and (B) microphotograph of the liver showing fibrin rich thrombi in the larger hepatic vein

- *Prof S Jain:* Despite the presence of a few oddities in this case, the diagnosis of a prothrombotic state during life was difficult and treating the patient with antitubercular therapy was justified.

COMMENTRY

The important issues in this case are the prothrombotic state of this patient causing widespread venous (brain/liver/ lungs) and also arterial thrombosis (brain/heart), its early age of manifestation, the relation of this prothrombotic state with pregnancy, and its masquerade as tuberculous meningitis with vasculitis. The brain was maximally affected with multiple infarcts leading to intractable seizures and the demise of the patient. The possibilities in this case are a prothrombotic state because of pregnancy along with an unknown inherited deficiencies of various anticoagulants (protein C/S/antithrombin), factor V leiden or a primary/ secondary APLA syndrome.

Venous thromboembolism is the commonest vascular disease.[4] Most commonly, it manifests as pulmonary embolism or deep venous thrombosis. Arterial thrombosis is relatively less common and mostly occurs as a complication of ruptured atheromatous plaque. Different acquired and inherited factors predispose to venous thrombosis and some of them also predispose to arterial thrombosis as well. Trauma or fractures and major orthopedic or oncologic surgeries are strong acquired risk factors for venous thrombosis (odds ratio >10) whereas pregnancy or puerperium, hypercoagulable state and antiphospholipid antibody syndrome constitute a moderate risk factor (odds ratio = 2-9).[4] Different inherited causes of thrombophilia include inherited deficiency of protein C or protein S, factor V leiden, prothrombin G20210A and antithrombin deficiency among many others. The antiphospholipid antibody syndrome is one of the most important acquired risk factors for thrombosis characterized by the presence of circulating antiphospholipid antibodies.[5] It can be associated with both arterial and venous thrombosis and/or complications of pregnancy, namely fetal loss.[4] Hyperhomocysteinemia is a mild risk factor due to metabolic defect and is capable of causing both arteriovenous thrombosis. The inherited causes, like factor V leiden or prothrombin G20210A, are due to point mutations making the clotting factors resistant to enzymatic degradation.[4] In addition, inherited thrombophilia can also result from quantitative and/or qualitative deficiencies of different natural anticoagulants like protein C, protein S and antithrombin.[4]

Pregnancy heralds modification of numerous hemostatic factors leading to a hypercoagulable state. Of the different hemostatic factors, an increase in the procoagulant factors or a decrease in the coagulation inhibitors or fibrinolytic factors lead on to a prothrombotic state.[6] Many procoagulant factors, like fibrinogen, Von Willebrand factors, factor II, V, VII, VIII, IX, X, XI, XII, XIII, are all increased in pregnancy along with a decrease in protein S which acts as a natural anticoagulant *in vivo*.[6] The serum level of fibrinolytic tPA is reduced and the serum level of fibrinolytic inhibitors like PAI-1, PAI-2 and TAFI is increased.[6] This altered physiology in pregnancy promotes thrombosis during pregnancy. Naturally, most of the other causes of ischemic stroke in young also loom large during pregnancy in addition to some pregnancy-specific causes of ischemic stroke like pre-eclampsia and eclampsia, choriocarcinoma, peripartum cardiomyopathy, amniotic fluid embolization and postpartum cerebral angiopathy.[6] Antiphospholipid antibody syndrome is again noteworthy as this can present with pregnancy-related complications namely fetal loss, is an important risk factor for thrombophilia and in addition can also be associated with microangiopathic features explaining greater prevalence of HELLP syndrome in these patients.[7]

HELLP syndrome is characterized by hemolysis, elevated liver enzymes and low platelet count.[8]

Thrombophilic states can be great mimicker of other diseases. Cerebral venous thrombosis is increasingly common disease and it can present with many nonspecific symptoms and signs, including headache, raised intracranial tension and focal neurological deficits. But, all these lack specificity and localization complicating the diagnostic dilemma.[9] This diagnostic difficulty can be further compounded by the fact that different other conditions also potentiate formation of venous and or arterial thrombosis. Even tuberculosis can cause venous thrombosis and complicate the scenario.[10] A thorough search of literature does not yield another case report to suggest a diagnostic dilemma between tuberculous meningitis with vasculitis and a prothrombotic state; however, the disease-mimicry of organ-specific or systemic thrombosis is widely mentioned in literature. This autopsy report suggests another diagnostic possibility in a suspected case of tuberculous meningitis in a young patient, not responding to treatment and/or with minor oddities.

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