Clinical Protocol

A 40-year-old lady presented with history of recurrent severe non-radiating mid-abdominal pain and loss of appetite and weight for 30 days, and progressive abdominal distension and fever for 15 days. In the last 4 days, she developed non-bilious vomiting, eight to ten times per day. She developed altered sensorium 2 days prior to hospital admission. Ascitic fluid was tapped by a local physician and she was told to have abdominal tuberculosis, for which she received treatment for 15 days. The fever subsided, but abdominal pain and distension increased gradually. She was noticed to have jaundice a few days prior to hospital admission. There was no history of altered bowels, GI bleed, seizures, headache, or swelling of feet or decreased urine output. She was married and has four children. There was no record of her menstrual cycle.

She was diagnosed to have sputum-positive pulmonary tuberculosis 4 years back, and had received treatment for 9 months. Thereafter she had had multiple episodes of fever with no localization.

Clinical examination

She had an average build and nutrition. The pulse rate was 80/min, blood pressure 114/80 mmHg, and respiratory rate 18/min. She had icterus, and ascites and hepatomegaly (liver span 16 cm). She was afebrile, jugular venous pressure was not raised and there was no clubbing or lymph node enlargement. Liver was palpable 2 cm below the costal margin with a span of 16 cm; spleen was not palpable. Bowel sounds were sluggish; rectal examination was normal. Cardiovascular system was normal. Respiratory system revealed vesicular breath sounds with few scattered crepts. Examination of central nervous system revealed grade IV encephalopathy; pupils were normally reacting with normal fundi, plantars were bilaterally flexors and deep tendon reflexes were exaggerated. There were no meningeal signs and no apparent deficit.

Investigations

Platelet count was high (4.4×10^9/L). Peripheral blood smear showed anisocytosis, occasional target cells, mild hypochromia with microcytes. The differential WBC count was normal. Serum cholesterol was 32 mg/dL, serum calcium/phosphate were 8.5/3.5 mg/dL, blood sugar ranged between 45 and 187 mg/dL. ESR, amylase, AST, ALT and serum alkaline phosphatase were within normal range. CSF: Protein was 15 mg/dL and sugar was 67 mg/dL, no cells. Urine revealed eight to ten RBC and two to three pus cells per high power field. Ascitic fluid had protein 2.1 g/dL, SAAG 1.8, ADA 9 units and sugar 55 mg/dL; microscopy showed 5000 cells, all were degenerated and intact neutrophils; there were no malignant cells or RBC. Culture was sterile. ECG showed sinus bradycardia. Arterial blood gas study was initially normal and terminally the patient had mild hypoxemia and respiratory acidosis.

Radiology

Chest X-ray showed small calcified lesions in both upper lobes. Abdominal X-ray showed multiple air-fluid levels. Ultrasonography of abdomen showed mild hepatomegaly with ascites. Contrast-enhanced computerized tomography (CECT) of the head was normal. CECT abdomen done 2 days after admission, showed mild hepatomegaly with enlarged caudate lobe and diffuse heterogeneous

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This case was discussed in the CPC forum of PGIMER, Chandigarh. The clinical protocol was presented and discussed by Chawla; radiological findings were discussed by Kalra and the pathology protocol was presented by Vaiphei. The session was chaired by V Sakhuja.
attenuation of the liver parenchyma. Branches of the hepatic veins were not visualized. The inferior vena cava appeared chinked due to caudate lobe indentation. There was minimal ascites and bilateral basal pleural thickening. Caudal sections showed thrombosed left and right branches of portal vein with collaterals (left > right [Fig. 1A and 1B]), and thrombus extending into main portal, splenic and superior mesenteric veins. The superior mesenteric artery was patent (Fig. 2). The spleen, pancreas and kidneys were normal. There was mural thickening of hepatic flexure, descending and sigmoid colon, and multiple polypoidal luminal protrusions in the region of ascending colon. The cecal wall was diffusely thickened with contrast tracking the lumen. Diffuse mural thickening of small intestinal loop was seen. Mesentery showed marked congestion with multiple enlarged lymph nodes (Fig. 3). The radiologic diagnosis was Budd Chiari syndrome (BCS) with portal, superior mesenteric and splenic vein thrombosis, and mesenteric ischemia. Cecal findings were suggestive of ischemia with evidence of ascites and mesenteric lymphadenopathy.

### Course in hospital

The patient was admitted with features of subacute intestinal obstruction. She was treated with ceftriaxone and antihepatic coma regime. Anti-tuberculous therapy was modified to ciprofloxacin and ethambutol on the basis abnormal liver function tests. She developed respiratory distress and was intubated. Subsequently she had persistent hypotension and was started on inotropes. She remained hypotensive and deeply comatose, and died after 6 days of hospital stay.

### Unit’s diagnosis

Old treated pulmonary tuberculosis; subacute intestinal obstruction and ascites: tubercular or malignant; hepatic and portal vein thrombosis with liver failure (BCS). Encephalopathy: metabolic or sepsis-related. Anti-tubercular drug-induced hepatitis.

### Discussion on Clinical Protocol

The clinical data in this lady would suggest a primary diagnosis of BCS based on the presenting symptom,
high-SAAG ascites, firm and enlarged liver, and gradually worsening prothrombin time. CECT showing an enlarged caudate lobe with hepatic vein thrombosis.

In acute BCS, the patient may present with a fulminant clinical course with severe abdominal pain, tender hepatomegaly, ascites, jaundice and rapidly worsening liver function. Patients who present with acute symptoms usually have poor outcome and survive for few days or weeks. Radiologically, liver is enlarged, smooth and congested with no caudate lobe enlargement. The chronic form of BCS is more commonly seen and presents with features of decompensation, ascites and collaterals. Radiology would demonstrate enlarged caudate lobe in >90% of cases. Asymmetrical atrophy or enlargement of one lobe of the liver is seen in >50 of cases. Besides the blockage in the hepatic veins in this patient, radiology demonstrated extensive blockage of portal system extending to superior mesenteric vein. These venous changes were associated with bowel wall thickening (ischemia/infarction) involving both small and large bowel.

Superior mesenteric vein thrombosis results in bowel ischemia. If it occurs in isolation, it is usually due to a hypercoagulable state. In association with thrombosis of portal vein, there could be portal hypertension. The index case had features of portal hypertension besides the venous occlusion, as indicated by high-SAAG ascites and collaterals. Colonic pathology in portal hypertension could be variable; colonic wall abnormality is seen in 35–40% of cases. Isolated or focal right-sided involvement of 6 mm to 3 cm in length could be seen in up to 25% of cases. Isolated small bowel wall thickening in such setting could be seen in 70–80% of cases. Higher frequency of colonic changes has been observed when superior mesenteric venous thrombosis coexists with portal hypertension.

The underlying conditions for occlusive diseases of hepatic, splenic or portal venous system could be an inherited disorder resulting in hypercoagulable state like deficiency of anti-trypsin III, protein C or S, mutation in factor V Leiden or prothrombin genes (Table 2). Acquired conditions include myeloproliferative disorders, paroxysmal nocturnal hematuria, anti-phospholipid syndrome, certain malignancies, pregnancy and administration of oral contraceptives. Local conditions which could result BCS are liver abscesses, hydatid disease, hepatocellular carcinoma, portal vein injury or inferior vena cava web. In some cases definite underlying or associated condition may not be detectable. Any intra-abdominal infective condition

Table 2  Etiology of Budd Chiari syndrome at three centers

<table>
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<th>Mumbai 6</th>
<th>Chandigarh 7</th>
<th>France 8</th>
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<tbody>
<tr>
<td>Number of cases</td>
<td>86</td>
<td>119</td>
<td>36</td>
</tr>
<tr>
<td>Antiphospholipid syndrome</td>
<td>11%</td>
<td>34%</td>
<td>14%</td>
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<td>Factor V Leiden mutation</td>
<td>26%</td>
<td>6%</td>
<td>31%</td>
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<tr>
<td>Fibrinogen II mutation</td>
<td>0%</td>
<td>26%</td>
<td>6%</td>
</tr>
<tr>
<td>Protein C deficiency</td>
<td>13%</td>
<td>38%</td>
<td>19%</td>
</tr>
<tr>
<td>Protein S deficiency</td>
<td>6%</td>
<td>32%</td>
<td>6%</td>
</tr>
<tr>
<td>Anti-thrombin III deficiency</td>
<td>4%</td>
<td>3%</td>
<td>0%</td>
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**Budd Chiari syndrome**

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Sluggish portal blood flow or procoagulant state

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Thrombosis of portal, splenic and superior mesenteric veins

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Bowel ischemia and spontaneous bacterial peritonitis

**Flowchart** Plausible sequence of the disease process
A possibility of abdominal tuberculosis needs to be considered as there was a past history of pulmonary tuberculosis. An active disease could result in a prothrombotic state resulting in hypercoagulable state. There were enlarged mesenteric lymph nodes. There were certain odd points for a diagnosis of abdominal or intestinal tuberculosis like diffuse bowel involvement without any functional disturbance and normal adenosine deaminase. Hepatocellular carcinoma is unlikely as there was no evidence of cirrhosis or any space-occupying lesion. Jaundice could be primary as in BCS, or a result of anti-tubercular therapy or sepsis. The significant hypocholesterolemia is difficult to explain. It could be seen in chronic malnutrition secondary mal-absorptive condition in chronic intestinal ischemia, in a critically ill patient, chronic liver disease or chronic long standing infections. Cause of death would be hepatic failure contributed by sepsis.

**Final clinical diagnosis**

Acute BCS (hepatic vein block); acute portal and superior mesenteric vein thrombosis and bowel ischemia; spontaneous bacterial peritonitis; hepatic failure either due to BCS or anti-tuberculous therapy, and sepsis.

**Open Forum**

**Das**: All procoagulants are synthesized in the liver. Most commonly encountered abnormal factors are anti-thrombin III, protein S or C. In the setting of primary liver injury, there would be reduction in the level of these factors. Hence these patients are not investigated during the acute or fulminant phase of liver injury. These tests are undertaken at least one month later. Alternatively, one could screen for anti-cardiolipin antibody by a rapid screening method twice at a gap of 6 weeks.

**Suri**: CECT demonstrated marked edema of sigmoid colon with non-visualization of mesenteric veins, suggesting possibility of thrombosis of inferior mesenteric vein as well.

**Jadav**: In an emergency surgical setting, diagnosing acute superior mesenteric vein thrombosis leading to bowel wall infarction is a difficult situation. This patient could have infarction-related bowel wall perforation, resulting in peritonitis, septicemia and shock.

**Pathology Protocol**

A complete autopsy was done. There was yellowish discoloration of the skin. Peritoneal cavity contained about 900 mL of straw-colored fluid. There was no evidence of external hemorrhage.

**Lungs** (weight 680 g): There was bilateral pleural thickening, more marked towards the basal region. Both upper lobes and right middle lobe showed cavities measuring 10–15 mm in size, containing cheesy material. Surrounding lung parenchyma showed patches of fibrosis. Microscopy of the fibrocavitatory lesion showed central areas of necrosis surrounded by fibrocollagenous tissue and chronic inflammatory cell and lymphoid aggregate, no epithelioid cell granuloma or giant cell response. Necrotic tissue showed acid-fast bacilli on ZN staining. Hilar and carinal lymph nodes were enlarged measuring ~10 mm; cut section showed caseous necrosis and calcification. Microscopy of the lymph nodes showed necrosis surrounded by fibrocollagenous tissue and chronic inflammatory cell response.

**Liver** (weight 1200 g): Mildly enlarged with thick capsule. Cut surfaces appeared blotchy and bile stained with patches of exaggerated mottling; whitish linear streaks and linear collagen bands were identified. The left lobe appeared more shrunken than right lobe. The sub-lobular veins were occluded by both organized and fresh thrombi. Caudate lobe was grossly enlarged with multiple fresh thrombi in small vessels and showed marked exaggeration of the mottling (Fig. 4A and 4B). All the major hepatic veins were occluded by organized thrombi (Fig. 5). Multiple sections from different areas showed random and confluent loss of liver parenchyma and many vessels thrombosed by both fresh and organized thrombi. These areas were fresh and hemorrhagic. There were older organized areas with loss of hepatocytes, expanded portal tracts with bridging, marginal bile duct proliferation and infiltration by moderate amount of inflammatory cells which were mixed in nature. Masson’s trichrome staining highlighted the random fibrosis within the liver parenchyma as greenish blue coloration. These areas showed extensive reticulin collapse and condensation along with dominant perportal regenerating hepatocytes resulting in reverse lobulation. Sections from the central veins including main hepatic veins showed occlusion by organized thrombi, which was highlighted on elastic-stained section. Some of the portal tracts were involved in the process of necrosis and regeneration. Uninvolved ones showed features of portal triaditis. Some of the portal tracts showed bile duct proliferation along with cytoplasmic, canicular and ductular cholestasis. Thrombotic process apparently involved the portal vein mainly by fresh thrombi at hilum of the liver extending to involve splenic and superior mesenteric veins.

**Spleen** (weight 180 g): Firm, congested with complete occlusion of the splenic vein by fresh thrombus. Microscopy: Capillarization of the splenic sinusoids with
marked depletion of the white pulp; the sinusoids contained many neutrophils.

**Intestine:** Small intestine had long gangrenous segment. Large intestine showed both fresh congested and firm thickened segments. Microscopy confirmed presence of fresh thrombi in the segmental small intestinal arcades. Sections from the large intestine revealed features of both fresh hemorrhagic changes and old ischemia in the form of submucosal fibrosis and fat infiltration. Superior and inferior mesenteric veins and their tributaries were completely occluded mainly by fresh and partly by organized thrombi. **Esophagus** showed deep ulceration with muscle necrosis. **Stomach** showed erosions with submucosal dilated vascular channels.

**Mesenteric lymph nodes:** sinus histiocytosis with erythrophagocytosis and vascular transformation of the sinuses.

**Kidneys (240 g):** Morphological changes of early acute tubular necrosis.

**Heart (185 g):** Epicardial petechial hemorrhages.

**Bone marrow:** Hypercellular with megablastosis.

**Final autopsy diagnosis**

1. Acid-fast bacilli-positive fibrocasaceous tuberculosis of lungs and hilar lymph nodes, and early bronchopneumonia.
2. Hepatic venous outflow tract obstruction with portal hypertension, thrombosis of portal, splenic and mesenteric veins.
3. Ischemic entero-colitis.
4. Erosive esophagitis and gastritis.
5. Acute tubular necrosis.

**Open Forum**

**Jain:** Blockage of both portal and hepatic venous systems has been demonstrated at autopsy. The intestinal infarct appeared to be an acute process.

**Jha:** What was the underlying cause for the thrombosis? Even after a thorough work-up for a hypercoagulable state, an abnormal underlying factor had been demonstrated in
only about 50% of cases. It would be interesting to know whether pulmonary tuberculosis was active with viable bacilli or a quiescent disease with viable or dead bacillus. Presence of pulmonary tuberculosis could be a possible factor for production of a hypercoagulable state.

Vaipehi: Active tuberculosis with hypercoagulable state could be an incidental association. The underlying procoagulant state in many of these tuberculosis cases with deep vein thrombosis recorded in literature was not known as they had not been worked-up.

Chawla: Association of a pro-coagulant state is with active tuberculosis, not with inactive tuberculosis. If one looks into the various series on BCS with a clinical presentation of acute episode, morphologically it has been always been a combination of acute and chronic changes, as in the index case. This case also had features of chronicity like regenerating nodules and reverse lobulation. Bowel infarction possibly had not occurred when the ascitic fluid tapping was done, two days prior to the demise of the patient. Hence, the bowel ischemia appears to be a terminal event, responsible directly for the demise of the patient.

Jain: The low cholesterol level could possibly be the result of chronic malnutrition. Certain genetic disorders like abetalipoproteinemia could result in low cholesterol level, and this patient did not have signs and symptoms of other system involvement like central or peripheral nervous system. With such a low cholesterol level, one could hypothesize possibility of a paradoxical thrombotic state.

Singh: Although there is no evidence that the tuberculosis was active in this patient, there are reports where tubercular protein producing vasculopathy in experimental animal model, resulted in further activation of the immune system by the activated T-helper cells producing cytokines.

Yadav: Contrary to common belief, ascitic fluid may not be blood–tinged in many patients with a gangrenous bowel. To document or exclude the presence of intestinal infarct, it is mandatory to subject the patient to a laparoscopic examination or mini-laparatomy. Mesenteric venous infarct is a distinctive clinical condition that could be differentiated from an arterial thrombosis. Bloody stool is a non-specific feature as is non-blood-tinged ascitic fluid.

Sakhuja: Could adequate anticoagulation therapy have saved this patient? There must be significant time interval between the onset of thrombosis of hepatic vein and that of portal vein.

Chawla: Adequate anticoagulation might have saved her from the progressive thrombotic episodes resulting in bowel infarction.

**Designation and affiliation of participants**

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M Singh: Additional Professor, Department of Pediatrics

**References**