A 45-year-old man was admitted for 11 days in the hospital. He was an alcoholic, consuming in cirrhogenic doses, who presented with i) cough and expectoration associated with low-grade, intermittent fever for 45 days; ii) progressively increasing breathlessness for the same duration; iii) increasing abdominal distension and jaundice for 30 days; and iv) altered sensorium for the last 3 days. There was no history of orthopnea or paroxysmal nocturnal dyspnea. There was history of decreased urine output for the last 4 days, which was associated with swelling of both the feet. There was no history of upper gastrointestinal bleed in the recent past, focal neurological deficit or seizures.

He had presented to the emergency department 4 years ago with hematemesis, and was diagnosed to have alcoholic cirrhosis and portal hypertension with esophageal varices. The varices were eradicated by regular endoscopic sclerotherapy, and he was on secondary prophylaxis with β blockers. Thereafter there had been no recurrence of bleed. He was on follow up at the institute for the next 2 years and then was lost to follow up. He was also diagnosed elsewhere to have pulmonary tuberculosis 5 years back and had taken anti-tubercular therapy for 3 months; following that he discontinued treatment on his own.

On examination, the patient was drowsy, restless and irritable. His pulse rate was 102 per minute, regular; blood pressure was 128/80 mmHg. He had pallor, icterus, clubbing, pedal edema and flaps. There was no lymphadenopathy. He had tense ascites. Liver and spleen were not palpable. Per rectal examination was normal. Examination of the respiratory system revealed centrally located trachea with diminished movement of the right chest wall. Percussion note was impaired in the right infra-scapular and infra-axillary areas. Bronchial breath sounds were heard in the left mammary region. The cardiovascular system was clinically normal. He was disoriented and irritable, with down-going planters.

**Investigations (Tables 1-4)**

Sputum for AFB: positive; HBsAg and anti-HCV: negative; urine spot Na+: nil; HIV serology: negative; ECG: sinus tachycardia.

**Radiology (Lal)**

Chest X-ray in October 2001: Left dome of diaphragm and left lung hilum appeared pulled up. Streak shadows were seen radiating from the left hilum indicating parenchymal fibrosis. There was a nodular calcified density in the left upper lobe indicating old focus of tuberculosis.

### Table 1: Hemogram

<table>
<thead>
<tr>
<th>May 31, 2001</th>
<th>February 11, 2005</th>
<th>February 15</th>
<th>February 16</th>
<th>February 21</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb (g/dL)</td>
<td>6.8</td>
<td>9.7</td>
<td>9.2</td>
<td>9.3</td>
</tr>
<tr>
<td>Leukocytes (/cmm)</td>
<td>19,500</td>
<td>8000</td>
<td>5900</td>
<td>7000</td>
</tr>
<tr>
<td>N/L/E/M</td>
<td>80/141/5</td>
<td>6820/3/3</td>
<td>7225/1</td>
<td>6626/5/3</td>
</tr>
<tr>
<td>Platelets (/dL)</td>
<td>Adequate</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Decreased</td>
</tr>
<tr>
<td>Peripheral blood film</td>
<td>Anisocytosis</td>
<td>Anisocytosis</td>
<td>Anisocytosis</td>
<td>Normocytosis</td>
</tr>
<tr>
<td>ESR (1st hour)</td>
<td>56</td>
<td>55</td>
<td>60</td>
<td></td>
</tr>
</tbody>
</table>

### Table 2: Blood biochemistry

<table>
<thead>
<tr>
<th>July 7, 2001</th>
<th>February 11, 2005</th>
<th>138/3.9</th>
<th>1304.1</th>
<th>1363.0</th>
<th>1344.0</th>
<th>1424.7</th>
<th>1323.9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na/K (mEq/L)</td>
<td>134/3.9</td>
<td>136/3.0</td>
<td>134/4.0</td>
<td>142/4.7</td>
<td>132/3.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urea/creatinine (mg/dL)</td>
<td>45/0.8</td>
<td>65/0.7</td>
<td>50/2.0</td>
<td>90/1.8</td>
<td>90/2.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilirubin (Total/Direct) (mg/dL)</td>
<td>4.2/1.4</td>
<td>3.5/2.1</td>
<td>4.2/1.4</td>
<td>5.6/2.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AST/ALT (U/L)</td>
<td>12/16</td>
<td>10/11</td>
<td>17/14</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alkaline phosphatase (KA units)</td>
<td>31</td>
<td>12</td>
<td>7</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protein (Total/Albumin) (g/dL)</td>
<td>5.8/2.6</td>
<td>6.9/2.7</td>
<td>6.9/2.4</td>
<td>6.9/2.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ca²⁺/IP (mg/dL)</td>
<td>9.3 / 3.2</td>
<td>9.0 / 4.0</td>
<td>8.6 / 5.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood sugar (mg/dL)</td>
<td>115</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amylase (SU)</td>
<td>160</td>
<td>133</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PT index (%)</td>
<td>43</td>
<td>86</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

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multiple smaller nodular shadows in the left mid zone indicating small patches of consolidation or miliary tuberculosis. X-ray chest in 2005 revealed almost similar small nodular opacities, which appeared to have increased in number and size, indicating pneumonia. There was persistence of calcified foci with evidence of cavitation. There was diffuse haze overlying the mid and lower zones of the right lung, indicating right-sided pleural effusion. Right dome of diaphragm could not be commented on.

**Ultrasonography** (October 2001): Liver enlarged, nodular outline with lobulated contour. Caudate and left lobes hypertrophied; intrahepatic biliary radicals normal. Spleen measured 10.6 cm. Hepatic veins and inferior vena cava were normal; portal vein measured 11 mm in diameter with few collaterals at the porta. Intraportalineal free fluid demonstrated. In 2005, liver was shrunken, measuring 9 cm, nodular in outline, with coarse echotexture and irregular surface. Portal vein measured 9.8 mm in diameter. Spleen measured 12.6 cm. There was ascites with right-sided pleural effusion. Hepatic veins were attenuated but lumen could be identified.

**Contrast-enhanced CT chest (2005):** Multiple fibrocavitatory lesions with surrounding consolidation in left lung with shift in mediastinum towards left. A 3 cm x 2 cm calcified lesion was identified in left apical region. Centrilobular areas showed nodules in tree-bark distribution in both the lungs. There was right-sided pleural effusion with ascites. Sections at the level of dome of diaphragm (Fig 1) showed multiple nodular densities, which are likely to be esophageal varices. Liver had nodular outline with heterogeneous attenuation. Similar nodular densities were also identified lower down around esophagus. Non-contrast CT head was normal.

**Course and management**

Five liters of straw-colored ascitic fluid was drained at paracentesis. The patient was managed with anti-hepatic coma regimen (lactulose and antibiotics). Sensorium improved and he was put on diuretics. Following this he had daily urine output of 800-1450 mL. After pulmonary consultation and contrast-enhanced CT scan of chest, a diagnosis of lung abscess was made and the patient was given cefotaxime, metronidazole and levofloxacin. Following this he remained afebrile throughout the hospital stay. Since sputum was positive for acid-fast bacilli, he was started on anti-tubercular therapy on February 19, 2005, comprising isoniazid 200 mg, rifampicin 450 mg, ethambutol 800 mg and pyrazinamide 1000 mg per day.

The next day he had tonic-clonic seizures, left focal followed by generalized. Following this his sensorium deteriorated. He was intubated and put on AMBU ventilation. After neurology consultation phenytoin was added; non-contrast CT head was normal. Subsequently he developed hypotension and became oliguric. Investigations showed increasing serum bilirubin and deranged renal function tests. Central line was inserted with an opening central venous pressure (CVP) of 7 cm of water. He was given supportive measures with intravenous fluids but he remained hypotensive. Inotropes (dopamine and noradrenaline) were added. Maximum systolic blood pressure achieved was 80 mmHg. Isoniazid, rifampicin and pyrazinamide were withdrawn. Drug dosages were modified as per renal function. He failed to respond to these measures and remained unconscious and hypotensive with worsening liver and renal functions. On February 23 he had cardiac arrest, from which he could not be revived.

**Unit’s final diagnosis**

- Alcoholic liver disease, decompensated cirrhosis with portal hypertension
- Disseminated tuberculosis (pulmonary and pleural)
- Sepsis

**Cause of death: septic shock**

**Discussion**

**Clinical protocol (Bhasin)**

The patient’s parameters tell us that he had disease involving the hepatic, pulmonary, pleural and possibly also the central nervous systems. The questions

---

**Table 3: Acid-base gas analysis**

<table>
<thead>
<tr>
<th></th>
<th>February 15, 2005 (room air)</th>
<th>February 18 (oxygen)</th>
<th>February 20 (AMBU)</th>
<th>February 21 (AMBU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.50</td>
<td>7.44</td>
<td>7.28</td>
<td>7.20</td>
</tr>
<tr>
<td>PaO₂ (mmHg)</td>
<td>45</td>
<td>51</td>
<td>108</td>
<td>66</td>
</tr>
<tr>
<td>PaCO₂ (mmHg)</td>
<td>29</td>
<td>34</td>
<td>51</td>
<td>64</td>
</tr>
<tr>
<td>HCO₃⁻ (mEq/L)</td>
<td>22</td>
<td>22</td>
<td>23</td>
<td>25</td>
</tr>
<tr>
<td>SaO₂ (mmHg)</td>
<td>85%</td>
<td>88%</td>
<td>97%</td>
<td>88%</td>
</tr>
<tr>
<td>BE (mEq/L)</td>
<td>+0.3</td>
<td>-0.9</td>
<td>-4</td>
<td>-5</td>
</tr>
</tbody>
</table>

**Table 4: Fluid analysis**

<table>
<thead>
<tr>
<th></th>
<th>Ascitic fluid</th>
<th>Pleural fluid</th>
</tr>
</thead>
<tbody>
<tr>
<td>February 11, 2005</td>
<td>10</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>Leukocytes (/cmm)</td>
<td>No WBC</td>
</tr>
<tr>
<td></td>
<td>Differential</td>
<td>L₉₀₀</td>
</tr>
<tr>
<td>Protein (g/dL)</td>
<td>0.06</td>
<td>1.39</td>
</tr>
<tr>
<td>Sugar (mg/dL)</td>
<td>98</td>
<td>93</td>
</tr>
<tr>
<td>Culture</td>
<td>Sterile</td>
<td>Sterile</td>
</tr>
<tr>
<td>Amylase (SU)</td>
<td>160</td>
<td>180</td>
</tr>
<tr>
<td>ADA (U/L)</td>
<td>104</td>
<td>180</td>
</tr>
</tbody>
</table>
that come to mind are: What was the etiology of the liver disease? Could alcohol be the only etiology? Did he subsequently acquire an additional insult to have suddenly progressed very rapidly? In alcohol-related cirrhosis, the caudate and left lobes are less commonly affected, sometimes resulting in small right lobe with left and caudate lobe hypertrophy. The other condition could be acute-on-chronic Budd-Chiari syndrome. Distinctive differences were noted in the characters of the patients with hepatic vein thrombosis we have seen before and after 1990 (Table 5).

Initially (i.e., in 2001) the index case had enlarged and nodular liver with patent hepatic veins and ascites on ultrasonography. In January 2005, he presented with features of portal hypertension with tense ascites, shrunken and nodular liver, with encephalopathy. Radiology revealed partially occluded hepatic veins.

The second set of symptoms was in relation to the pulmonary system. With his clinical and investigative findings the possible diagnosis would be fibrocaseous pulmonary tuberculosis with intra-parenchymal and right pleural spread. In order to complete the list of cavitated lesions in the lung, we need to mention cavitary malignancy, either primary (scar carcinoma developing in AFB-positive tuberculosis) or metastatic, and fungal infection, either primary or as superadded infection. For a metastatic lesion, there was no clear-cut focus for the primary except for the liver nodules. However the liver nodules were radiologically similar. A primary lung tumor with secondary liver nodules is unlikely as the liver was nodular for the last 4 years.

The tense ascites that the patient developed recently suggests a recent additional cause. These could be one or more of the following: tuberculosis, malignancy, pancreatic ascites, cardiac ascites, and worsening of chronic liver disease. In the recent past, there was no acute exacerbation of the symptoms and there was no association with raised liver enzymes, excluding the possibility of superadded viral or alcoholic hepatitis. Tuberculous hepatitis could be considered; in this condition, liver enzymes could be normal or near normal but usually with raised alkaline phosphatase level.

Another condition that could be considered is superimposed venous thrombosis of either the portal vein or the main or terminal hepatic veins. Based on the imaging studies, obstruction of the portal or main hepatic veins could be excluded. Hepatocellular carcinoma would be unlikely as there was no rise in alkaline phosphatase and no evidence of any mass or nodular lesion on radiological examination.

The next question is, why the decompensation? It could be due to multiple factors: massive upper gastrointestinal bleed, superimposed viral hepatitis, alcoholic hepatitis resulting in central hyaline sclerosis, granulomatous hepatitis, hepatocellular carcinoma, or superimposed vascular pathology involving the portal or hepatic veins. Occlusion of terminal venules could result in veno-occlusive disease (VOD) or a sinusoidal obstruction syndrome, which result clinically in tense ascites, jaundice and encephalopathy.

**Final diagnosis**
- Alcoholic liver disease with portal hypertension
- Central vein obstruction or sinusoidal obstruction syndrome (veno-occlusive disease)
- Superimposed hepatocellular carcinoma
- Fibrocavitatory tuberculosis of the lungs and pleura with multi-organ dissemination

**Differential diagnosis**
- Disseminated fungal infection

**Cause of death**
- Adrenal crisis secondary to involvement by disseminated tuberculosis

**Sequence of disease process**
- Liver injury resulting in tense ascites, jaundice, encephalopathy and pre-terminal azotemia
- Disseminated tuberculosis of bone marrow resulting in persistent anemia and thrombocytopenia; intracranial involvement resulting in seizure; adrenal gland involvement resulting in persistent hypotension
- Disseminated tuberculosis leading to hypercoagulable state

**Open house forum**
**Singh:** This appears to be a case of alcoholic liver disease (cirrhosis) with pulmonary tuberculosis. Fol-
Following institution of the anti-tubercular therapy, the symptoms appeared to have worsened. Persistent hypotension could due to adrenal involvement by tuberculosis.

Chairman: I would like to exclude secondary amyloidosis due to long-standing tuberculosis. Amyloidosis usually involves the kidneys but is unusual in other sites.

Nanda: A disseminated fungal infection could have similar clinical presentation and the terminal event could be the result of fungal infection, besides VOD of liver.

Gupta: There is no denying the diagnosis of tuberculosis. However, pulmonary tuberculosis for 5 years is unlikely. The chest X-ray appearance of calcified round shadow in the left upper lobe is too perfect for an old focus of tuberculosis. A possibility of pulmonary hamartoma could be considered. He had persistently low hemoglobin for the last five years; persistent anemia secondary to tuberculosis involving the bone marrow would be rather odd.

Chairman: The radiology picture appears to be classical for tuberculosis; besides, the patient had AFB-positive sputum.

Suri: There is no doubt about the diagnosis of pulmonary tuberculosis. Associated fungal infection remains the differential diagnosis.

Pathology protocol (Vaiphei)

The patient was subjected to a complete autopsy. The liver (Fig 2) weighed 1200 g and appeared shrunken and firm. The outer surface was partly nodular. The cut surfaces showed exaggerated mottling, discolored by patches of bile staining and congestion with intervening pale areas. Caudate lobe was grossly enlarged resulting in compression of the inferior vena cava and hepatic vein openings. Portal vein appeared dilated. The large-sized blood vessels did not contain any thrombus.

Histology (Fig 3) from pale and depressed areas revealed loss of normal lobular pattern of liver. In some of these areas, there was total replacement of the liver lobule by collagenized tissue with apparent preservation of sinusoidal pattern and lobular architecture. The relationship and architecture of the portal tract and central veins could be perceived in these affected areas. The terminal hepatic and sublobular veins were occluded by thrombi of varying age, some organized and others more recent. Organized thrombi were concentrated in the hyalinized areas and more recent thrombi were seen more in relatively less affected areas of the liver parenchyma (Fig 4). Structures within the portal tract were well maintained; only the portal vein at the hilum showed intimal plaque (Fig 5). Hepatocytes in preserved areas looked normal. Stigmata of alcoholic liver disease in the form of fatty change, satellitosis, perivenular or pericellular fibrosis could not be demonstrated in the unaffected areas. Hyaline sclerosis of central veins was identifiable in the areas where there was loss of liver parenchyma and replacement by collagenized...
tissue. There were neither any features of active tuberculosis nor hyalinized nodules of healed tubercles. There was no evidence of cholestasis.

The spleen was mildly enlarged, weighing 280 g. There was depletion of white pulp with evidence of sinusoidal capillarization. The esophagus and gastric fundus had submucosal varices.

Both lungs weighed 1200 g, which is grossly overweight. The left pleura had thick exudate and was firmly adherent to the parietal wall. The left bronchial tree showed evidence of bronchiectasis and lumen contained discolored exudative material. Left lung showed a cavity measuring 3 cm x 3 cm x 5 cm towards the basal region of upper lobe, with irregular shaggy margin containing necrotic material. Multiple smaller fibrocous foci measuring ~1 cm were also identified in the left lower lobe. Scarring was seen in the left apical region. Right lung and pleura looked much healthier. The entire right lung parenchyma felt sub-crepitant.

Histology of the left lung and abscesses showed abscess wall formed by epithelioid cell granulomas with areas of necrosis. The abscesses were positive on Ziehl-Neelsen staining for acid-fast bacilli. Some of the granulomas were breaking into the bronchial tree and resulting in tuberculous bronchopneumonia. Blood vessels around the areas of granulomatous response showed evidence of endarteritis obliterans. Patches of interstitial fibrosis were also present. Right lung showed evidence of diffuse edema and multiple miliary tubercles with microscopic foci of necrosis. Left pleura and superior surface of diaphragm were covered by fibrin-rich exudative granulomatous inflammation, which showed positive staining for acid-fast bacilli. Pulmonary hilar and carinal lymph nodes measured ~2 cm in diameter and cut section showed areas of caseous necrosis. Microscopy showed evidence of epithelioid cell granulomas with areas of necrosis that stained positive for acid-fast bacilli.

Small and large intestine had multiple epithelioid cell granulomas in the mucosa and submucosa, which were negative on Ziehl-Neelsen staining. All throughout the gastro-intestinal tract, the lamina propria had increased number of dilated mucosal capillaries.

Bone marrow showed erythroid hyperplasia with megaloblastosis and evidence of hemophagocytosis. Bone trabeculae showed changes of osteopenia.

Heart weighed 220 g. There was rounding of the left border indicating left ventricular free wall hypertrophy. Apical slices revealed concentric left ventricular hypertrophy; the wall measured 15 mm in thickness. There was dilatation of the right ventricular and atrial cavities. Both right and left atrioventricular valves showed hemodynamic changes. Microscopy showed variation of myocardial fiber size with anisonucleosis and focal degenerative changes of muscle fibers. There was increase in lipofuscin pigment. Coronaries were essentially normal. Aorta showed changes of grade II atherosclerosis.

Kidneys together weighed 260 g. Both kidneys were grossly normal. Microscopy revealed changes of vacuolization of the proximal convoluted tubules. Glomeruli, blood vessels and interstitium had essentially normal morphology.

He also had diffusely enlarged thyroid gland and showed features of goiter at microscopy.

There was evidence of chronic malnutrition as indicated by brownish discoloration of myocardium with increased lipofuscin pigment in the myocardium, reduction in epicardial fat with mucinous degeneration and marked reduction in mesenteric fat.

**Final autopsy diagnosis**

1. AFB-positive fibrocavitatory tuberculosis of left lung and tuberculous bronchopneumonia and bronchiectasis with miliary spread to right lung and intestine. Tuberculosis of pulmonary hilar and carinal lymph nodes
2. Veno-occlusive disease of liver with evidence of portal hypertension in the spleen, esophagus and stomach, and ascites

**Open house forum**

**Jindal:** It would be interesting to highlight the disparity of findings on radiology and pathology. Radiology projected multiple small nodular lesions in the right lung with pleural effusion. The autopsy findings showed florid tuberculosis in the left lung but no effusion. Besides, tuberculosis is not a known cause for hypercoagulable state.

**Vaiphei:** Hypercoagulable state has been observed in various conditions including tuberculosis. These
reports are either as single case reports or in small series. The exact cause-and-effect relationship has not been well understood. The increasing reported incidence could be related to more awareness and availability of equipped laboratories. There was no effusion in the left pleura; rather, it had thick fibrinous exudates all over.

Chairman: How much of the liver disease could have been contributed by the alcohol intake?

Vaiphei: Alcohol generally does not produce such kind of liver disease, though VOD can sometimes be seen in relation to alcohol intake.\(^5,6,7\) Indigenously manufactured liquor has been observed to contain high level of heavy metals like arsenic. These toxic metals could be responsible for some of the liver disease in a genetically predisposed individual. Besides, the patient was on anti-tubercular therapy.

Gupta: I do not think that tuberculosis predisposes to the development of a hypercoagulable state. The history of anti-tubercular drug intake was also only for 3 months; he possibly was not on these drugs for the last 5 months. Hence they could not be responsible for the VOD the patient had and it is very unlikely that they produce VOD.

Bhasin: There is no reference of tuberculosis producing VOD. However, there are many reports of hypercoagulable state in tuberculosis. There were two papers incriminating tuberculosis as a cause for deep venous thrombosis.\(^3,8\) One needs to study and analyze these cases further.

Vaiphei: We are ignorant of the treatment this patient received before he came to us.

Jindal: The hypercoagulable state described in literature is usually with disseminated tuberculosis or active infection. In these cases, the patients had features resembling disseminated intravascular coagulopathy resulting in acute respiratory distress syndrome. I do not think inactive tuberculosis would result in hypercoagulable state. One of the known hematological disorders related to tuberculosis and anti-tubercular therapy is thrombocytopenia.

Dhiman: Perivenular dominant sclerosis with loss of liver parenchyma is well known in alcoholic liver disease and alcohol-related VOD,\(^7\) but changes of alcoholic liver disease would be demonstrable in such a setting. The perivenular sclerosis in the index case was extensive; the parenchyma otherwise did not show any evidence of alcoholic liver disease. Besides alcohol, this patient must likely have suffered effects of some toxic agent, which resulted in extensive damage and loss of liver parenchyma. The patient may have taken some herbal medicine. We have seen this in our day-to-day practice where patients take herbal medicines to ameliorate their problems but instead have adverse effects on their liver.

Singh: Besides arsenic and pyrrolizidine alkaloid, anabolic steroids and oral contraceptives could result in hypercoagulable state. But we do not have enough history to support these hypotheses.

References