A 33-year-old woman presented with fever for 10 days, jaundice for 2 days, altered sensorium for 2 days, and decreased urine output for 1 day. The fever initially responded to antipyretics. She was investigated elsewhere. Since Widal test was positive for H (1:160) and O (1:160) antigens, she was treated as enteric fever (details not known). The fever decreased but persisted. On the third day after the medication, she was disoriented, and later had grand tonic-clonic seizures with no residual neurological deficit. Clinically, she did not have cholestatic features, bleeding manifestation or cola-colored urine. Biochemical tests showed raised bilirubin levels.

At admission, she was obese and had tachycardia. She was mildly pale and jaundiced, with no cyanosis, lymphadenopathy or pedal edema. Cardiovascular examination was normal. She had bilateral vesicular breathing with no added sounds. Central nervous system examination showed a conscious but disoriented patient (E3M5V1). Flaps were present but there was no neck rigidity or focal neurological deficit. All reflexes were normal. Per abdomen, the liver was soft, palpable 2 cm below the right costal margin (span 14 cm). Spleen was not palpable.

Investigations

Hemoglobin level dropped from 12 g/dL to 4.3 g/dL in a week; WBC count rose from 12000 to 16400/dL (>70% polymorphonuclear). Platelets dropped from adequate to 19000, then rose to 77000/dL.

Blood sugar level was high. Serum electrolytes were normal. Blood urea and creatinine (3.4 to 5.4 mg/dL) levels increased gradually over the week. Serum bilirubin level increased from 5.6 (direct 4.2) to 10.5 (7.7) mg/dL. Serum proteins, AST, ALT, alkaline phosphatase, calcium, phosphorus, uric acid and magnesium levels were normal or near normal. Prothrombin index increased from 63% to 86% and activated PTT dropped from 42% to 26%.

Other investigations showed

1. Urine: 15-20 pus cells per high-power field. Culture: no growth
2. Ultrasonography: liver span 17.6 cm; spleen, gall bladder, common bile duct and pancreas normal. No ascites. Kidneys normal except for blurred cortico-medullary differentiation
3. X ray chest normal
4. Blood culture sterile

Fever, jaundice, altered sensorium, with multiple systemic manifestations

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Course and management

The patient was put on anti-hepatic coma regime and antibiotics (IV ceftriaxone). Doxycycline and artesunate were stopped when the peripheral blood film and serology tests were negative for malarial parasite. The next morning, there was worsening of the sensorium following two episodes of convulsions, and the patient went into status epilepticus. She was continued on phenytoin, and later propofol and clobazam were added. Subsequently she had focal seizures, for which imaging was planned but could not be done because of hemodynamic instability. Worsening of the sensorium was associated with poor respiratory efforts, for which she was ventilated. Shock and circulatory collapse occurred on day 2 of hospital stay, and remained refractory for the rest of the hospital stay despite fluid resuscitation and inotropic support. She developed bilateral crepitations in the lungs and persistent hypoxemia even on 100% oxygen. Peritoneal dialysis was initiated in view of the persistent metabolic acidosis and oliguria. The hyperglycemia was managed with insulin.

She had progressive worsening and multi-organ dysfunction, to which she succumbed.

Unit’s final diagnosis

- Fulminant hepatic failure, probably hepatitis E virus (HEV) related
- Sepsis with multi-organ dysfunction

Discussion (Vikash Suri)

Based on the clinical data (short febrile illness, evidence of acute liver and renal failure, features of encephalopathy, anemia, thrombocytopenia and evidence of disseminated intravascular coagulopathy
[DIC], and refractory shock with multi-organ dysfunction), I would like to consider the following differential diagnoses:

**Acute liver failure (ALF)**

Since the clinical problems developed within 10 days, it suggests a possibility of hyperacute liver failure.\(^1\) In India, the major etiology of acute liver failure is viral (95%), commonly hepatitis E and B, with antitubercular drugs accounting for most of the rest.

Other conditions producing ALF include i) infections by Epstein-Barr virus, herpes simplex, cytomegalovirus, and hepatitis C, A and non A-E viruses; ii) Wilson’s disease; iii) Budd-Chiari syndrome; iv) acute fatty liver of pregnancy; v) autoimmune hepatitis; v) toxins; vi) malignant infiltration by lymphoma and other cancers; vii) ischemia, as in persistent hypotension and heat stroke; and viii) primary graft dysfunction.

Some conditions that could present with features of acute liver and renal failure are i) infections like hepatitis E, malaria, leptospirosis, enteric fever, scrub fever and typhus; ii) autoimmune hepatitis complicated by sepsis, and iii) infiltrative disorders.

The odd points for a diagnosis of HEV-related ALF are: i) not very high levels of transaminases, ii) coagulopathy that was correctable easily with vitamin K, iii) relatively high alkaline phosphatase level, iv) thrombocytopenia at admission, v) significantly low hemoglobin level and vi) hyperglycemia. At this point, I would like to discuss the significance of positive IgM anti-HEV.

False-positive HEV serology could occur in normal individuals (as documented in blood donors), patients with hepatitis other than hepatitis E, and chronic liver disease including primary biliary cirrhosis.

**Severe falciparum malaria**

Points that would favor this diagnosis include the enlarged liver, mildly elevated transaminases, early development of coma, associated renal failure, progressive anemia, DIC and thrombocytopenia at presentation, and adult respiratory distress syndrome (ARDS). Important points against the diagnosis include fever responding without antimalarials, absence of splenomegaly or coagulopathy, no demonstrable parasite in the peripheral blood film, and negative serology. Malarial hepatitis has been observed to simulate fulminant hepatic failure (FHF), but can generally be differentiated from viral causes.\(^2\)

**Icteric leptospirosis**

This patient did not have important clinical features for the diagnosis, like conjunctival suffusion, severe prostration, and positive serology. Features that were present (hepatomegaly, abnormal liver function tests, thrombocytopenia, leukocytosis, renal failure, aseptic meningitis, DIC and mildly raised alkaline phosphatase) could also be seen in icteric leptospirosis.

**Typhoid fever**

This is one strong possible diagnosis in this patient as she had positive Widal test. She was given some antibiotics and apparently had shown response, though she developed CNS complication on day three. On further investigation, she was found to have abnormal liver function tests. She also had mildly abnormal coagulation profile. The temporal profile of the illness would favor a diagnosis of typhoid fever. Certain features, like absence of enlarged spleen, no leukopenia, presence of relative bradycardia, deep coma and complication in the first week, do not favor a diagnosis of typhoid fever. A negative repeat Widal test after hospitalization could be due to the medication received earlier.

With recent reports of emergence of resistant *Salmonella typhi*, one could expect to see more patients with typhoid having unusual response to standard medications. A high percentage of salmonella infections, especially in children, has been found to be associated with myocardial dysfunction.\(^3,4\)

**Rickettsial-scrub typhus**

The points that would favor this diagnosis include the residence of the patient, i.e., Himachal Pradesh, the season of the illness, presentation with fever, and onset of complication after the first week. Presence of jaundice, anemia, renal failure, meningoencephalitis, ARDS, DIC and shock, all would favor the diagnosis. But absence of rash, eschar, lymphadenopathy, and negative Weil-Felix test would be strong evidence against the diagnosis.

**Final clinical diagnosis**

- Typhoid fever or leptospirosis resulting in acute liver failure, with hepatitis E co-infection
- Sepsis (bacterial or fungal), DIC, multi-organ dysfunction syndrome (MODS), ARDS and renal failure
Cause of death: cerebral edema and/or intracranial bleed and MODS

Pathology protocol

At the time of autopsy, the prosector noted yellow discoloration of the skin. Peritoneal cavity had 500 mL of yellowish clear fluid. Pleural and pericardial cavities were normal.

Liver (weight 1670 g) was enlarged, fatty and bile stained. Microscopically, the lobular architecture was preserved. Hepatocytes showed extensive macro- and microvesicular fatty changes. Portal tracts were fibrosed, with occasional bridging fibrosis. They were expanded by variable amount of inflammatory cells comprising lymphocytes, plasma cells, histiocytes and occasional neutrophils. Histiocytes and lymphocytes showed focal periportal and intralobular collections, with hepatocytic destruction, forming the classic typhoid nodules (Fig 1). These lymphocytes were positive for CD3 (T-cell type) on immunohistochemistry (Fig 2). There was marked Kupffer cell hyperplasia with evidence of hemophagocytosis (Fig 3). Lymphocytes were scattered within the liver parenchyma, extending to the hepatic capsule. There was intrahepatic and intracanalicular cholestasis.

Heart (weight 310 g) was enlarged with loss of epicardial fat. There was concentric left ventricular hypertrophy and patches of myocardial discoloration. Microscopically, sections from both sides showed diffuse interstitial edema and infiltration by mononuclear inflammatory cells composed of lymphocytes, plasma cells and macrophages, with necrosis of individual myofibers. Inflammatory cells were also seen infiltrating the endocardium and epicardium. These lymphocytes are positive for CD3 on immunohistochemistry.

Kidneys (weight 300 g) were bilaterally enlarged and swollen, pale, with easily stripped capsules. Cut sections revealed distinct corticomedullary junction and marked medullary congestion. Pelvicalyceal system was well maintained. Microscopically, glomeruli had normal morphology. Interstitium showed heavy patchy inflammatory cell infiltration with evidence of tubular destruction and no fibrosis. The inflammatory cells were composed of lymphocytes, plasma cells, histiocytes and few neutrophils. Tubules were dilated and contained hyaline, granular and pigment casts. Blood vessels were normal. No fibrin thrombi or mesangial cell response was noted in any of the sections studied.

Spleen (weight 290 g) was mildly enlarged. Histology revealed depletion of the white pulp. Sinusoids were expanded by histiocytes with evidence of hemophagocytosis along with many extramedullary hemopoietic cells.

Mesenteric lymph nodes were enlarged with hemorrhagic cut surface. Microscopically, there
was depletion of lymphoid tissue with sinus histiocytosis showing hemophagocytosis.

**Bone section:** marrow was hypercellular, with all three lineages seen and predominance of erythroid precursors. There was prominence of histiocytic cells showing hemophagocytosis.

**Lungs** (weight 840 g) were overweight and sub-crepitant with patchy hemorrhagic consolidated area in the left upper lobe. Microscopically, fresh intra-alveolar hemorrhages were seen, with hyaline membrane formation and early bronchopneumonia.

**Stomach:** in the pylorus along the greater curvature, there were two 3-cm grossly congested friable plaque lesions (Fig 4). Cutting through the lesion, there was transmural discoloration of the gastric wall with friability. Microscopy of sections from the lesion revealed transmural necrosis of the gastric wall. There was minimal inflammatory cell response with many fungal profiles within and outside the blood vessels, along with fibrin.

Morphology of the fungal profiles was consistent with that of mucormycosis (Fig 5).

**Intestines** grossly and microscopically showed prominence of Payer’s patches, with no ulceration or evidence of hemophagocytosis.

**Final autopsy diagnosis**

A young lady with positive Widal test with

1. Hemophagocytosis in liver, spleen, mesenteric lymph nodes and bone marrow
2. Typhoid nodules in liver with hepatitis
3. Concentric left ventricular hypertrophy with lymphocytic myocarditis
4. Tubulointerstitial nephritis
5. Diffuse alveolar damage, intra-alveolar hemorrhage and early bronchopneumonia
6. Gastric mucormycosis

**Comment**

The most common cause of typhoid fever is *Salmonella enterica* serotype typhi, although salmonella of other serotypes, particularly *S. enterica* serotype paratyphi A, can cause a similar enteric fever. Typhoid fever has probably been an important cause of illness and death for centuries, although historical accounts do not clearly distinguish it from other febrile illnesses. It has been implicated in the death of Alexander the Great, in 323 B.C. The causative organism is widespread in all parts of the world, although the disease is more prevalent in developing countries than in developed ones.

Typhoid fever is a systemic infectious disease, and gastrointestinal tract is the primary site. Numerous extra-intestinal complications and atypical presentations involving the central nervous system, cardiovascular system, pulmonary system, bones and joints, hepatobiliary system, genitourinary system and others have been documented.

Liver involvement is encountered in 80% of patients, and 60% develop mildly abnormal liver function tests. Severe hepatic involvement with clinical features of acute hepatitis can be seen in 1% to 26% of patients. Histologic findings are usually of non-specific reactive changes, in the form of Kupffer cell prominence, mild portal tract inflammation, and evidence of cholestasis. There may be focal hepatocytic necrosis with mononuclear cell infiltration forming the characteristic ‘typhoid nodule’. Recent demonstration of intact *Salmonella typhi* in liver tissue suggests that or-
ganisms are phagocytosed by the reticuloendothelial system but overcome the cell's killing action and produce hepatic injury by liberating cytotoxic substances in situ.\textsuperscript{7-9}

There have been reports of salmonellosis presenting with hepatitis, acute interstitial nephritis, myocarditis, cardio-pulmonary and other multi-organ involvement.\textsuperscript{10-13}

References


The case was presented and discussed in the staff clinico-pathological forum of the institute. The clinical protocol was discussed by Vikash Suri, Assistant Professor, Department of Internal Medicine, and pathology by Kim Vaiphei, Additional Professor, Department of Histopathology. The report was compiled by Vaiphei.