Clinicopathological Conference Report

Acute-on-chronic Liver Failure in a Young Lady

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CASE REPORT

A 25-year-old lady presented with a history of abdominal distension for 3 months and jaundice for 1 week. The patient was apparently asymptomatic 3 months back when she had spontaneous abortion at 4 weeks of gestation. Following this, she developed abdominal distension, which was insidious in onset and gradually progressed to bilateral pedal edema. There was no history of fever, decreased urine output, or bleeding manifestations, such as hematemesis or melena. There was no history of pruritus, passage of clay-colored stools, or colicky abdominal pain. History suggestive of altered sensorium or altered sleep rhythm was absent. The patient denied any history of previous blood transfusions or tattooing. There was no history of similar illness in the family. The patient had one child who was 18 months old and delivered by a lower uterine cesarean section, and the indication for the operation was not forthcoming.

On evaluation, the lady was found to have anemia with thrombocytopenia. An ascitic fluid analysis revealed a high serum ascites albumin gradient (SAAG) with low protein. The adenosine deaminase level in the ascitic fluid was within normal limits. There was no evidence suggestive of spontaneous bacterial peritonitis (SBP). Autoimmune hepatitis workup was negative for antinuclear antibodies, antismooth muscle antibodies, anti-liver-kidney microsome-1 antibodies, and anti-liver cytosol-1 antibodies. Viral serology for hepatitis B and C virus was negative.

EXAMINATION

On evaluation, she was pale, icteric, and had bilateral symmetrical non-tender pedal edema. There was absence of peripheral lymphadenopathy, cyanosis, or clubbing. The jugular venous pressure was not raised. She did not have any stigmata suggestive of chronic liver disease. Abdominal examination confirmed the presence of ascites, in the form of distension and shifting dullness. However, no dilated superficial veins were seen. There was no palpable organomegaly. Cardiovascular, respiratory, and central nervous system examination was normal.

INVESTIGATIONS

Peripheral smear (December 5, 2017): Macrocytic red cells admixed with few microcytes and normocyttes. Schistocytes 1% (Tables 1 to 6).

Urine routine (December 5, 2017): Normal

Hemolytic work-up (December 6, 2017):
- Plasma hemoglobin: Negative
- Urine hemoglobin: Negative
- Glucose-6-phosphate dehydrogenase: Not deficient
- Lactate dehydrogenase (LDH): 1,768 IU
- Reticulocyte count: 3.5%
- C-Reactive Protein:
  - (December 4, 2017): 21.1 mg/L
  - (December 6, 2017): 28.6 mg/L

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Procalcitonin (December 6, 2018): 2.1 ng/mL

Autoimmune profile: Negative surface antigen of the hepatitis B virus, Antihepatitis C virus, Antihepatitis A virus and Antihepatitis E virus: Negative

Serum ceruloplasmin: 11 mg/dL

Serum ammonia: 187 μg/dL

Ultrasonography:

(December 1, 2017): Ultrasonography and Doppler of splenoportal axis showed

- Coarse echotexture of the liver with surface nodularity. However, no focal lesions were present
- Spleen span was 12.7 cm
- Mild narrowing was seen at the cavoatrial junction

**COURSE AND MANAGEMENT**

This 25-year-old lady presented with spontaneous first trimester abortion followed by ascites, pedal edema,
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and jaundice. Initial evaluation at the medical outpatient department showed a high SAAG ascites with low protein, anemia, and thrombocytopenia. Upper gastrointestinal endoscopy revealed small esophageal varices and portal hypertensive gastropathy. On admission, the laboratory reports were consistent with the findings of anemia, thrombocytopenia, hypoalbuminemia, raised aspartate aminotransferase (AST) levels, coagulopathy, and normal renal function tests. A provisional diagnosis of decompensated chronic liver disease with jaundice and ascites was kept.

Subsequently, the patient was drowsy and developed fever. Ascitic fluid analysis was suggestive of SBP. The patient was shifted to gastroenterology intensive care unit and started on intravenous piperacillin, tazobactam, and metronidazole. Antihepatic coma measures were started in the form of rifaximin, lactulose, and intravenous albumin.

Two days later, the results showed sterile cultures and negative viral serology and autoimmune profile. She had persistent SBP which made her slip into grade III hepatic encephalopathy. The following day, the antibiotics were upgraded to meropenem and teicoplanin. The patient was intubated following the worsening sensorium. A bedside ultrasound Doppler did not show any evidence of cavoatrial junction. She developed features suggestive of disseminated intravascular coagulopathy (DIC). Her liver function tests worsened with falling alkaline phosphatase (ALP) levels. In light of the low serum ceruloplasmin levels, a possibility of Wilson’s disease was kept and the patient was started on D-penicillamine therapy. Hepatology consultation was sought and the patient’s relatives were counseled for liver transplantation.

On day 7 of admission, the lady developed renal dysfunction with oliguria and was started with intravenous terlipressin. Albumin infusions were continued and inotropic support was added as the patient went into shock. Sustained low-efficiency hemodialysis was started following a nephrology consultation. However, the same was interrupted due to deteriorating hypotension in spite of maximum inotropic support. She terminally developed refractory shock and succumbed to her illness in the early hours of day 8 of admission.

CASE ANALYSIS

This lady had an underlying chronic liver disease (nodular surface of the liver, increased portal vein diameter, splenomegaly, ascites, and varices) and presented with acute liver failure as evidenced by rise in bilirubin, raised enzymes, coagulopathy, and thrombocytopenia. There was an ongoing element of hemolysis as reflected by the presence of anemia, thrombocytopenia, raised mean corpuscular volume, increased reticulocyte percentage and LDH, hyperbilirubinemia, and hypersplenism.1

The thrombocytopenia with which the patient presented can be attributed to the underlying chronic liver disease or a possible secondary hemophagocytic lymphohistiocytosis (HLH).2,3 The index patient had four of the eight criteria required for a clinical diagnosis of HLH in the form of splenomegaly, cytopenias, hypertriglyceridemia, and raised serum ferritin.

Low serum ceruloplasmin (Table 7) can be seen in Wilson’s disease, Menkes disease, copper deficiency and aceruloplasminemia. Given the present context, a possibility of Wilson’s disease seems likely.4

The acute-on-chronic liver failure in the index case can be explained by an underlying cirrhotic liver with an additional insult of simmering Wilson’s disease with a cumulative effect due to the infection (in the form of SBP) (Flow Chart 1). The patient satisfied the Consortium Acute-On-Chronic Liver Failure in Cirrhosis definition.5

The SBP is the second most common cause of infection (Table 8) in patients with cirrhosis.6 SBP can be community-acquired or nosocomial in origin.7 The community-acquired SBP is defined as those which occur in patients who have not been previously hospitalized or received any kind of intravenous antibiotics or intervention. The nosocomial SBP is a difficult subset to treat which have been acquired in patients who had a history of hospitalization, intravenous antibiotics, or intervention in the last 3 months. The index case had a nosocomial acquired SBP. The choice of empirical antibiotic therapy, such as meropenem and daptomycin in treating nosocomial SBP has shown to be a stronger predictor of survival.8

The patient was likely to have underlying Wilson’s disease as its incidence is more common in this age group and gender.4 The patient’s laboratory profile also had indicators, such as a low ALP by total bilirubin (TB) ratio (less than 4), a high AST by alanine aminotransferase (ALT) ratio (more than 2.2), low serum ceruloplasmin, and evidence of hemolytic anemia.4

Of these, screening tools, such as AP/TB ratio of less than 4 and ALT/AST ratio of more than 2.2 have been shown to have a likelihood ratio of 23 and 7 for diagnosing fulminant Wilson’s disease. These indicators are important as serum ceruloplasmin may be falsely elevated in fulminant cases, being an acute phase protein.9

| Table 7: Causes of high and low serum ceruloplasmin |
|--------------------------|--------------------------|
| **High**                | **Low**                  |
| Copper/zinc toxicity    | Wilson’s disease          |
| Acute-phase reactant    | Menkes disease           |
| Alzheimer’s disease     | Copper deficiency         |
| Rheumatoid arthritis    | Aceruloplasminemia        |
| Lymphoma                |                          |

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Lastly, a concomitant hepatitis B infection cannot be ruled out as the occult infection has been shown to be responsible for cryptogenic cirrhosis and contributed to cases of fulminant hepatitis.10

**FINAL CLINICAL DIAGNOSIS**

- Acute-on-chronic liver failure, grade III
- Model for end stage liver disease-35, Child Turcotte Pugh score
- Acute insult: Spontaneous bacterial peritonitis, sepsis with DIC
- Chronic insult: Cirrhosis of liver, decompensated with ascites, SBP, encephalopathy
- Etiology: Wilson’s disease or occult hepatitis B infection
- Multiorgan failure
- Cause of death: Refractory shock

**CLINICAL DISCUSSION**

Chairperson: Request the treating unit senior resident for comments.

Senior Resident: The patient developed SBP following admission. The role of empirical and choice of antibiotic therapy in the absence of a positive culture report remains a point of discussion. However, the index case was initiated on a broad-spectrum intravenous antibiotic regimen.

Prof Usha Dutta: This case is a learning case for all residents. Wilson’s disease should be kept as a possibility in a young lady who presents with acute liver failure and having both viral and autoimmune markers to be negative. The reliability of serum ceruloplasmin is questionable, as it may be falsely high, being an acute-phase reactant, though serum ceruloplasmin was low in this case. The presenter has rightly highlighted the low values of ALP in patients with acute liver failure in Wilson’s disease. I expect features of Wilson’s on histopathology.

Chairperson: If no other comments are coming forth, I request Dr Manoj to please present the pathology protocol.

**PATHOLOGY FINDINGS**

A partial autopsy was performed. The prosectors noticed the deceased to be moderately built, icteric, had bilateral pedal edema, and abdominal distension. On opening the serous cavities, the peritoneal cavity yielded 4.5 L, pleural cavities yielded 200 mL each, and pericardial cavity yielded 180 mL of straw-colored fluid.

Liver: Weighed 1,250 gm and showed nodular capsular surface (Fig. 1A). The cut surface also showed nodules of varying size from less than 3 mm in diameter (micronodules) to more than 3 mm in diameter (macronodules) (Fig. 1B). The bile duct, portal vein, and inferior vena cava with hepatic vein opening were dissected and were found patent (Figs 1C to E). These nodules were bile-stained with the presence of whitish intervening areas corresponding to fibrous septae. Microscopy confirmed the mixed nodular cirrhotic pattern (Figs 2A to C). The fibrous septae were inflamed. There was marked fatty change with components of both microvesicular and macrovesicular steatosis (Fig. 2D). Many hepatocytes showed the presence of intracytoplasmic eosinophilic Mallory hyaline bodies (Fig. 2E). The portal tracts...
showed moderate-to-dense inflammation composed of lymphocytes and plasma cells (Fig. 2F). The central veins showed a slight increase in perivenular fibrosis. The hepatocytes showed marked intracellular cholestasis with the presence of bile plugs, which were highlighted by the emerald green color on Fouchet’s stain (Fig. 3A). Iron stores were slightly increased (Fig. 3B). The periportal hepatocytes showed a marked increase in cytoplasmic copper binding protein as shown by the coarse cytoplasmic cola-colored granules on orcein stain (Fig. 3C). There was also an extensive increase in elemental copper within the hepatocytes as shown by fine rose-colored cytoplasmic granules on rhodamine stain (Fig. 3D). Overall features were of mixed nodular cirrhosis secondary to Wilson’s disease.

Spleen: Weighed 280 gm, was enlarged with a tense capsule. Microscopy showed red pulp congestion with preserved white pulp. Overall features were of congestive splenomegaly.

Lungs: Weighed 850 gm and were heavy with a dull pleural surface. Cut surface shows consolidated areas in the right middle lobe and upper part of left lower lobes (Fig. 4A). Microscopy showed the alveolar spaces in the consolidated areas to be filled with foamy macrophages with septae showing congested capillaries (Fig. 4B). The bronchioles show the presence of aspirated vegetable matter and associated Gram-positive bacteria (Fig. 4C). Overall features were of aspiration pneumonia.

Kidneys: Weighed 410 gm with smooth external surface. The capsule could be easily stripped off. The cut surface was bile-stained with maintained corticomedullary differentiation (Fig. 5A). Microscopy showed normal glomerular histology. The tubules showed the presence of simplification of lining epithelium with the luminal shedding of epithelial cells (Fig. 5B). Many hyaline and bile casts were seen. The bile casts were better highlighted by the emerald green color on Fouchet’s stain (Fig. 5C). Overall features are of bile cast nephropathy.

Heart: Weighed 280 gm with a normal external surface. The right inflow, right outflow, and left inflow tracts were normal. The left outflow tract showed the presence of a patch of hemorrhage (Fig. 6A). Microscopy showed the patch of the hemorrhagic area to correspond to subendocardial hemorrhage (Figs 6B and C). The coronaries were patent with no evidence of atherosclerosis.

Bone marrow: Microscopy showed cellular marrow spaces with trilineage hematopoiesis and preponderance of erythroid lineage (Fig. 7).

Esophagus: Small varices were present.
Figs 2A to F: (A) Hematoxylin and eosin-stained section shows nodules of varying sizes with inflamed fibrous septae. (B) Reticulin stain highlighting the nodules. (C) Masson trichrome stain highlighting the fibrous septae outlining the nodules. (D) Hematoxylin and eosin-stained section shows marked macro- and microvesicular steatosis. (E) Hematoxylin and eosin-stained section shows eosinophilic intracytoplasmic Mallory hyaline bodies within the hepatocytes. (F) Hematoxylin and eosin-stained section shows portal tract with moderate-to-dense infiltration by lymphocytes and plasma cells.

Figs 3A to D: (A) Fouchet’s stain highlighting the emerald green canalicular and bile ductular cholestasis. (B) Perl’s stain highlighting the presence of iron in form of Prussian blue granules in the hepatocytes. (C) Orcein stain highlighting copper-associated protein in the periportal hepatocytes in the form of coarse cola-colored cytoplasmic granules. (D) Rhodanine stain highlighting elemental copper in the hepatocytes in the form of fine rose-colored cytoplasmic granules.
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Stomach, small intestine, and large intestine: No significant pathological findings were seen.

Mesentery: No significant pathological findings were seen.

Pancreas, adrenal, skin, skeletal muscle, and thyroid: No significant pathological findings were seen.

**FINAL AUTOPSY FINDINGS**

A 25-year-old with acute-on-chronic hepatic failure
- Mixed nodular cirrhosis secondary to Wilson’s disease
- Portal hypertension: Varices, ascites, and splenomegaly
- Bile cast nephropathy
- Aspiration pneumonia
- Subendocardial hemorrhage

**FINAL DISCUSSION**

Chairperson: Both the pathology and clinical protocols are open for discussion.

Speaker 1: Congratulations on an excellent demonstration of histopathology. I had a query regarding whether the diagnosis of Wilson’s disease can be made on histopathology alone or does it require the demonstration of the dry weight of copper on liver tissue.

Manoj: I do agree that certain books recommend estimating the dry weight of copper on liver tissue for making a diagnosis of Wilson’s disease. I had walked down to our Biochemistry department enquiring for the same, but this test is not being carried out at present. But given the clinical and histopathological features, Wilson’s disease remains the only differential diagnosis in the index case.

Prof Usha Dutta: As per the current guidelines, there is no requirement of demonstration of the increased dry weight of copper in the liver. The indices, such as low ALP and other liver function tests are sufficient in making a diagnosis of Wilson’s disease in a given context.

Prof Ashim Das: This type of portal tract inflammation is also seen in autoimmune hepatitis. However,
since we have standardized rhodamine, which is a stain for elemental copper in our department, we have been able to demonstrate the same, thereby supporting the diagnosis of Wilson’s disease. This was not possible a few years back. However, there were no features to suggest Budd–Chiari on autopsy.

Chairperson: Had a question for the pathologist. What would you attribute the cause of subendocardial hemorrhage?

Manoj: I did look for a possible association of subendocardial hemorrhage in the index case. However, subendocardial hemorrhage remains a nonspecific finding and can be attributed to vigorous cardiopulmonary resuscitation.

Chairperson: If there are no more comments, we conclude the CPC.

SUMMARY

This case is a reminder that an undiagnosed Wilson’s disease can be present in patients, especially young females as acute-on-chronic liver failure. In the absence of positive autoimmune and viral markers, clues should be
drawn from biochemical markers, such as ALP and bilirubin in making a diagnosis. The autopsy also highlights the extent of aspiration pneumonia in patients with blunted sensorium and hence caregivers should be sensitized to undertake more stringent measures to prevent the same.

REFERENCES