

# Clinicopathological Conference Report—PM 24433

## Fulminant Hepatic Failure: A Fatal Presentation of Wilson Disease

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*This case (PM 24433) was discussed on 30-03-2015, as a student clinicopathological exercise at PGIMER, Chandigarh, India.*

*Clinical details and case analysis: Avani Hegde (Department of Internal Medicine, PGIMER, Chandigarh, India)*

### CLINICAL DETAILS

Master A, 11 years old male, a resident of Indri, Haryana was admitted to the pediatric emergency with chief complaints of fever, yellowish discoloration of eyes and skin along with inappropriate behavior. The episode of fever occurred 20 days back and lasted for 10 days duration. Fever was high grade (documented at 102°F), intermittent and was relieved on taking medication. It was associated with nausea, vomiting, and malaise. The child had yellowish discoloration of eyes and skin since 20 days. This was progressive and was associated with passage of high colored urine and clay colored stools. He showed excessive irritability, use of abusive language/inappropriate words and alteration in sleep-wake cycle for 2 days. There was blurring of vision since 2 days. There was no history of headache, abnormal body movements, loss of consciousness or seizures. No history of bleeding from any site, rash, pruritus, decreased urine output or

breathing difficulty. There was no significant past history. There was no history of jaundice, intake of over the counter drugs, intake of desi medication, neurological or psychiatric illness. There was no history suggestive of autoimmune disease, blood transfusions or surgeries. There was no previous hospitalization. The child was born to nonconsanguineous Hindu parents with no history of neurological or psychiatric illness, no history suggestive of autoimmune disease and there was no history of epidemic of jaundice in the locality. The child was developmentally normal and doing well at school. His diet was home-based and he was a nonvegetarian. He was adequately immunized for age but was not vaccinated for hepatitis A and B.

### EXAMINATION

The pulse rate was 110 beats/min, respiratory rate 30/min, he was afebrile (temperature 37°C), blood pressure was 114/70 mmHg and the SaO<sub>2</sub> was 98%. His height was 124 cm (<3rd centile for age), weight was 26 kg (which was at 3rd centile for age), and the occipitofrontal circumference was 51 cm (which was 50th percentile for age). The child was irritable, agitated and subsequently he had posturing and abnormal body movements. There was deep icterus and pallor. There was no lymphadenopathy, edema, cyanosis or clubbing. There was no rash, scratch marks, he had shining nails and no obvious Kayser-Fleischer ring. There was no evidence of chronic liver disease. The abdomen was soft, nontender. The liver was palpable 2 cm below right coastal margin with a span of 9 cm. It was firm in consistency with regular margins and smooth surface. Spleen was not palpable. Traube's space was dull on percussion and bowel sounds were present. External

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genitalia was normal. The respiratory system was normal with equal air entry on both sides. No crackles or wheeze was heard. The cardiovascular system was within normal limits. No murmurs were heard. On neurologic examination, the Glasgow coma score was E3M6V4. The child had stage 2 encephalopathy. Pupils were bilaterally symmetrical, 3 mm and reactive to light. The tone and power were normal. Deep tendon reflexes were exaggerate and bilateral plantars were upgoing. The sensory system was normal. There were no meningeal signs.

## INVESTIGATIONS

The hemogram showed normocytic normochromic anemia with Hb of 11.7 gm/dl. There was a preterminal fall in Hb to 9.6 gm/dl and peripheral blood showed anisocytosis, microcytes, elliptocytes, hypochromic RBCs and no malarial parasite. There was neutrophilic leukocytosis with a total leukocyte count of 14,800 cells/ $\mu$ l. The platelets were adequate, (324000/ $\mu$ l). There was intravascular hemolysis and plasma Hb was 165 mg/dl, blood cultures were sterile, G6PD levels were normal and the direct coomb's test was negative. The biochemical workup showed a total serum protein of 7.5 gm/dl. There was conjugated hyperbilirubinemia with a total bilirubin of 22.9 mg/dl and conjugated fraction of 16.6 mg/dl. The AST was 492 IU/l and ALT was 490 IU/l. The alkaline phosphatase was 377 IU/l. Coagulogram was deranged (PT 68 sec, INR 7.8, aPTT 88 sec, qualitative D dimer was positive. There was dyselectrolytemia with Na of 159 meq/l and K was 3.4 meq/l. The serum creatinine was 0.4 mg/dl and increased to 2.7 mg/dl preterminally. Ultrasonography (USG) of abdomen showed a liver size of 15 cm with hyper-echoic heterogenous echotexture and a normal outline. The portal vein was 12 mm with mild periportal echogenicity. The gallbladder was contracted with edematous wall. Spleen measured 11.2 cm. The splenic vein was 10 mm, dilated with few collaterals at splenic hilum. There was mild ascites. The impression was of liver parenchymal disease with splenomegaly and mild ascites, suggestive of portal hypertension. Work-up for viral hepatitis including anti-HAV IgM, anti-HEV IgM, anti-HCV IgM and HBsAg were negative. The autoimmune hepatitis work-up including autoimmune hepatitis markers ANA, SMA, LKM, PCA, AMA were negative. The serum ceruloplasmin was low 9 mg/dl (Normal >20 mg/dl). The urine copper was 699  $\mu$ g/24 hours (normal <40  $\mu$ g/24 hours).

## COURSE IN THE HOSPITAL

The child presented with stage 2 hepatic encephalopathy and measures to control intracranial pressure in form of mannitol and 3% NaCl were used. Lactulose and rifaximin were added for liver failure. Following this, the child

developed seizures and was started on phenobarbitone and levetiracetam. Hepatic encephalopathy progressed from stage 2 to 4. There was derangement of coagulation profile for which fresh frozen plasma was given. The pneumonia was treated with ceftriaxone, sulbactam and metronidazole. Later vancomycin, piperacillin and amphotericin B were added. Phenytoin was also given. Patient developed acute kidney injury with hypernatremia which was treated with peritoneal dialysis. He developed shock, inotropes were given but could not be resuscitated. The unit's clinical diagnosis was acute liver failure with grade 2 hepatic encephalopathy with a strong possibility of Wilson disease.

## CASE ANALYSIS

In this 11 years boy, previously normal with acute onset jaundice followed by encephalopathy and coagulopathy, features are of acute liver failure with hemolysis, acute kidney injury and healthcare associated infection. The child had high bilirubin, moderately elevated aminotransferases with AST more than ALT and severe coagulopathy. He had hemolytic anemia with a negative coombs test and a normal G6PD. The serum ceruloplasmin was low and urine 24-hour copper excretion was high. The USG of abdomen showed altered liver echotexture with splenomegaly and dilated splenoportal axis. The points of discussion are as follows:

*Acute liver failure:* This is often a fatal event in children. The etiology varies with age and geographical location. A study on etiology of fulminant hepatic failure from PGIMER showed hepatitis A in 58% cases, hepatitis B in 4.6%, hepatitis E in 4.6% and a coinfection of hepatitis A and E in 4.6%. Other infections contributed in 4.6%. Wilson disease was the cause in 4.6% and autoimmune hepatitis in 2.3% cases.<sup>1</sup>

The etiologies to be considered in the current setting include the following:

*Infectious:* Hepatitis A, B and E, herpes viruses can be associated with acute liver failure. The points in favor of a viral etiology are jaundice following a prodrome and acute hepatitis. Viral hepatitis is a common cause of acute hepatitis in endemic regions like India. But, the viral serology for hepatitis A, B, C and E were negative. Also, serum ceruloplasmin was low and the urinary copper excretion was high.

*Immune mediated:* Etiologies include—autoimmune hepatitis, macrophage activation syndrome and hemophagocytic syndrome. The acute presentation favors a possibility of autoimmune hepatitis. But, this was a male child and had no other features of autoimmune disorders. Autoimmune markers were negative.



*Drugs and toxins:* Acetaminophen overdose, valproate, isoniazid, halothane, amanita are common causes of acute liver failure. Though in this case, there was no history of intake of any drugs or indigenous medication. This seems to be highly unlikely.

*Ischemia and abnormal perfusion:* Budd-Chiari syndrome, congenital heart disease, cardiac surgery and severe asphyxia are highly unlikely in the present case.

*Metabolic disease:* Wilson disease is the most likely etiology in this case considering the age of onset, the acute presentation, very high serum bilirubin, Coomb's negative hemolytic anemia, low serum ceruloplasmin and high urinary copper excretion. Hepatic presentations of Wilson disease is variable and can include asymptomatic elevation of serum aminotransferase, steatohepatitis, acute hepatitis (20–25%), chronic hepatitis (26–30%), portal hypertension, cirrhosis (25–30%). Fulminant hepatic failure is the presentation in 10 to 15% of cases.<sup>2</sup>

## OPEN HOUSE DISCUSSION

*Chairperson:* Now I call the treating unit SR for their comments.

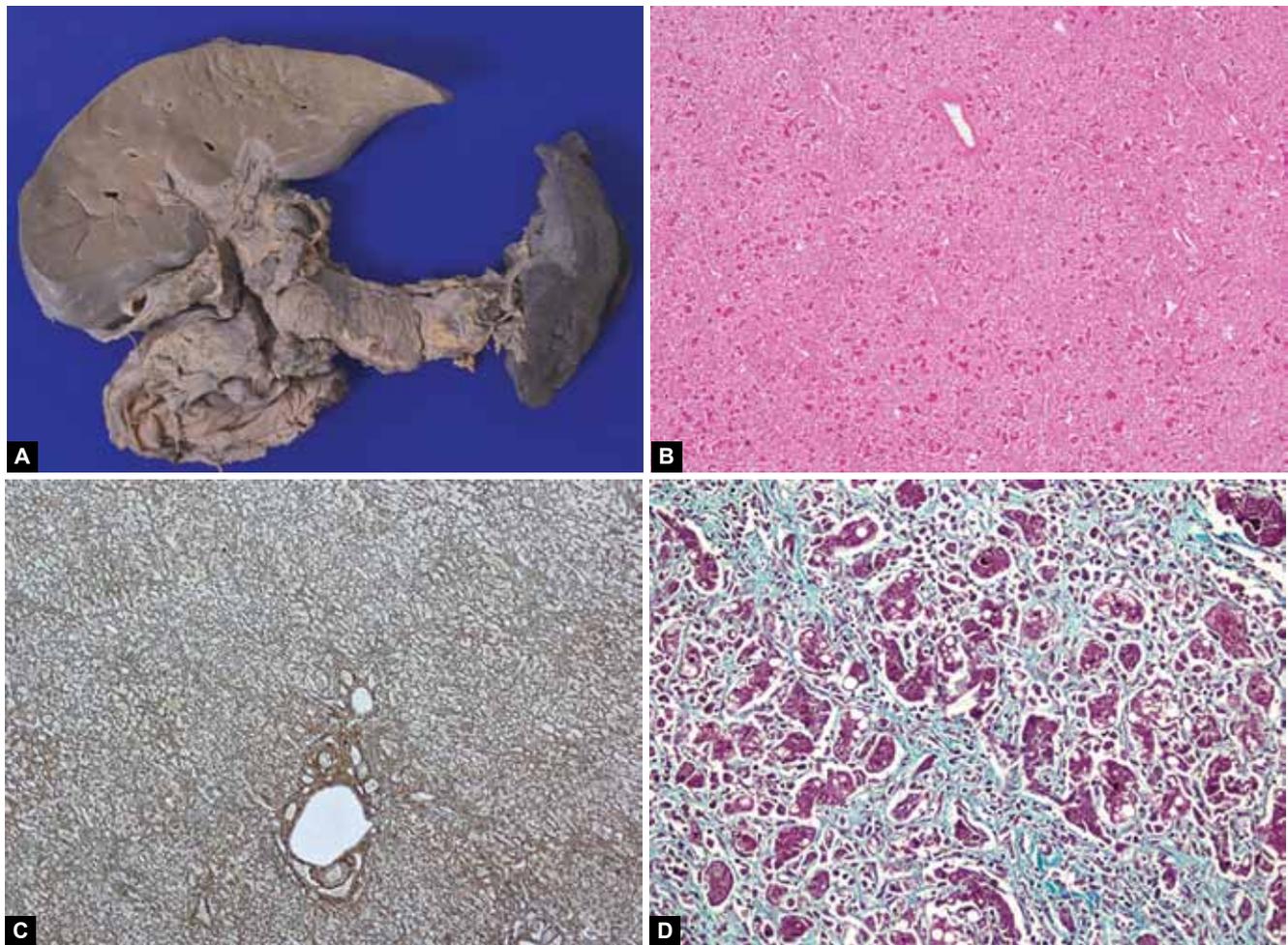
*Treating unit SR:* This child presented to us with acute liver failure and grade 2 hepatic encephalopathy. Work-up for autoimmune etiology and viral hepatitis was negative. Looking at the age of patient, fulminant presentation Wilson disease was high on cards. The work up was highly suggestive with low serum ceruloplasmin and high urinary copper excretion.

*Chairperson:* Now I call the pathology discussant to show the findings at autopsy.

### Autopsy Findings—PM 24433: Swathi Jogunoori

A partial autopsy was performed on this 11 years old child who was apparently well 1 month back. The prosectors noted that the patient was moderately built and icteric. The peritoneal cavity and bilateral pleural cavities yielded 500 and 300 ml of straw colored fluid respectively. The pericardial cavity was within normal limits. The liver weighed 690 gm and was small for age (Normal 909 gm). It was soft in consistency. The capsular aspect and cut surface did not show any focal lesions (Fig. 1A). Portal vein was dissected and it did not reveal any thrombosis or dilation. The biliary tree was within normal limits. The microscopic examination of liver showed distorted lobular architecture with extensive hepatocytic loss. There was massive, multiacinar confluent hepatic necrosis with few surviving hepatocytes (Fig. 1B). The collapse of reticulin framework was well appreciated on reticulin stain (Fig. 1C). Masson trichrome stain did not reveal any significant fibrosis (Fig. 1D). The

surviving hepatocytes showed micro and macrovesicular steatosis (Fig. 2A). Intracytoplasmic and intracanalicular cholestasis was noted (Fig. 2B). Occasional Mallory hyaline bodies were seen (Fig. 2C). Ballooning degeneration and focal pseudorosette formation was noted. Collection of lymphomononuclear and histiocytic cells is seen (Fig. 2D). There was mild kuppfer cell prominence. Orcein stain did not reveal any cola colored granules due to the paucity of surviving hepatocytes. The dry weight of copper was performed on the post-mortem liver tissue, which was within normal limits. CK7 immunostain highlighted areas of bile duct metaplasia. Immunostain for hepatitis B core and surface antigen were negative. Overall features were those of multiacinar confluent hepatic necrosis and with the serum showing low ceruloplasmin levels and high urinary copper excretion, findings were consistent with a diagnosis of Wilson disease. The dry weight of copper on the post-mortem liver tissue was within normal limits and this is possible as there were only few surviving hepatocytes. The spleen was enlarged and weighed 180 gm (normal 87 gm) (Fig. 1A). The capsular and cut surface were within normal limits. On microscopy, there was attenuation of white pulp and congestion of red pulp. The pancreas was grossly and microscopically within normal limits. The esophagus (Fig. 3A) showed mucosal congestion and dilated vascular spaces in the wall. These dilated vascular channels were confirmed on microscopy. The mucosa was essentially normal (Fig. 3B). The stomach (Fig. 3A) showed mucosal congestion. On microscopy, several dilated and congested vessels were identified in the submucosa indicating a portal gastropathy (Fig. 3C). The kidneys weighed 240 gm and capsular aspect was unremarkable. The cuts surface showed distinct corticomedullary junction. The glomeruli were essentially normal. The tubules showed features of acute tubular necrosis with flattening and distalization of the lining. Bile casts were seen in few of the tubules (Fig. 3D). The lungs weighed 880 gm and were heavy for age. The pleural aspect was dull and showed fibrinous tags. The tracheobronchial tree was within normal limits and did not show any ulceration or aspirated material. The lungs were firm to feel. The cut surface showed hemorrhagic solid areas (Fig. 4A). The pulmonary vessels were dissected and did not show any thrombi. There was diffuse pulmonary hemorrhage and edema on microscopy. Collection of polymorphs were seen in the interstitium which was extending into the alveolar spaces (Fig. 4B). Hyaline membrane formation was noted (Fig. 4C). Overall features were those of pneumonia with diffuse alveolar damage and pulmonary edema. The heart was grossly and microscopically within normal limits. The bone marrow showed adequate representation of all three hematopoietic elements.



**Figs 1A to D:** (A) Gross picture with slice of liver, spleen, pancreas and C loop of duodenum. Liver is shrunken and does not show any focal lesion. Spleen is enlarged, (B) microphotographs of the liver showing multiacinar necrosis (H&E 10x), (C) collapse of reticulin framework with no nodule formation (reticulin 10x) and (D) Masson's trichrome stain showing collapse (MT 20x)

*Final autopsy diagnosis:* PM 24433, 11 years male with acute liver failure and hepatic encephalopathy.

- Multiacinar confluent hepatic necrosis, consistent with Wilson disease (low serum ceruloplasmin levels, high urinary copper excretion).
- Features of portal hypertension: Ascites, esophageal varices, portal gastropathy.
- Confluent bronchopneumonia with pulmonary hemorrhage, edema and diffuse alveolar damage.
- Acute tubular necrosis and bile casts.

## OPEN HOUSE DISCUSSION

*Chairperson:* Protocol is now open to the house for discussion.

*Treating unit SR:* There is good clinic-pathologic correlation in this case. The autopsy did not reveal any cola colored granules on orcein stain. How do we explain this?

*Uma Nahar Saikia:* As there was confluent multiacinar necrosis, there were very scant surviving hepatocytes. Thus, no positivity for orcein or rhodanine was detected. The dry weight of copper was performed on the post-mortem liver tissue, which was within normal

limits. This can be easily explained by the extensive loss of hepatocytes.

*Senior resident:* Was there any significant fibrosis in the liver?

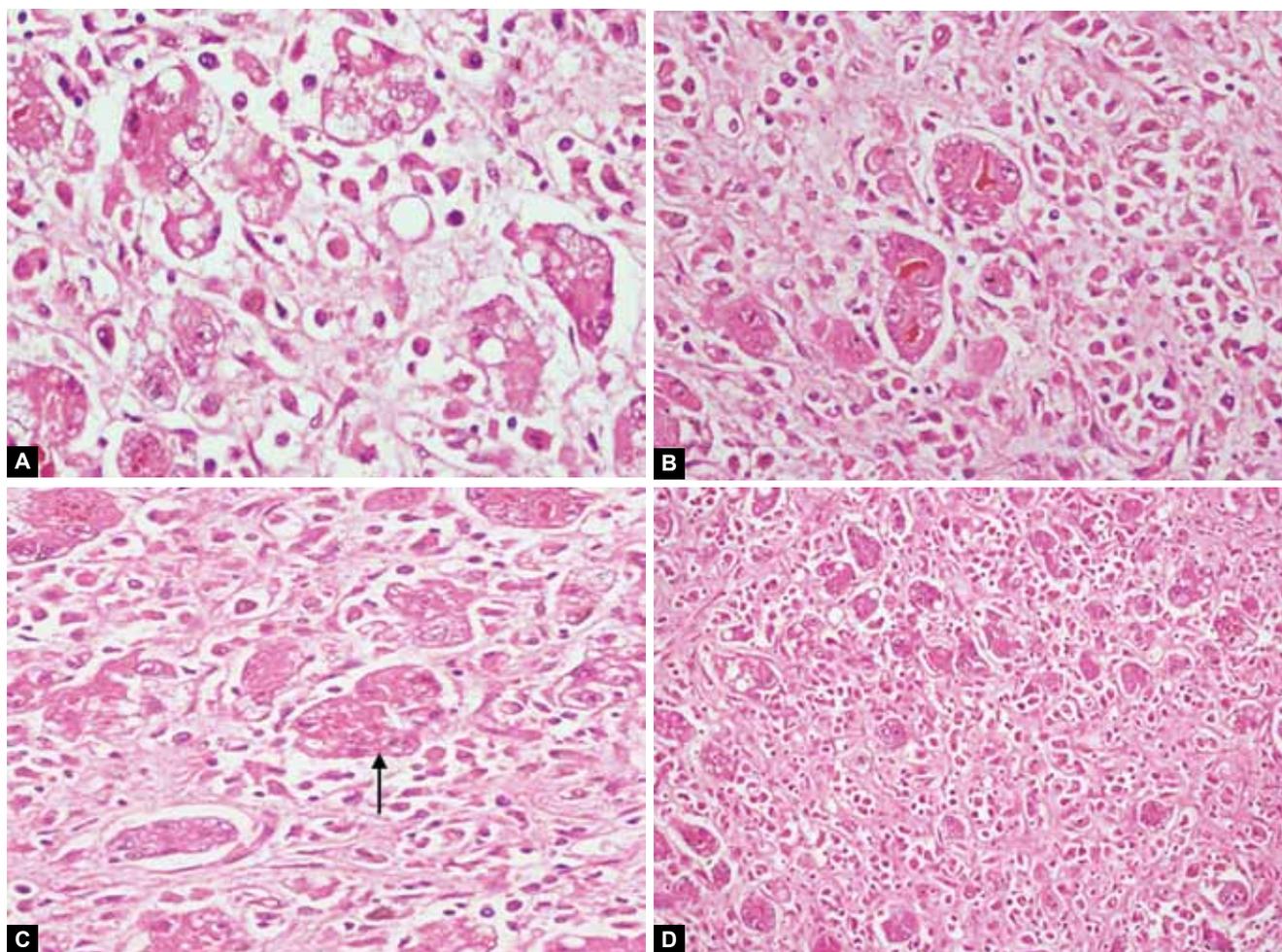
*Uma Nahar Saikia:* There were areas which showed some pericellular fibrosis on Masson's trichrome stain and thus, a possibility of Indian childhood cirrhosis was also being considered. But, looking at the entire clinical picture and the age of presentation, we favored a diagnosis of Wilson in the case.

*A Das:* There is no significant fibrosis on Masson's trichrome stain. The blue color we are seeing in the picture is just due to collapse of the framework.

*Meenu Singh:* A genetic testing for Wilson could have been done in the case. The other siblings also need to be tested as Wilson is an autosomal recessive disorder and every pregnancy has a 25% chance of getting affected.

## COMMENTS

Acute liver failure in children is a complex multisystemic illness that evolves quickly after a catastrophic insult to the liver. The clinical course is decided by the underlying



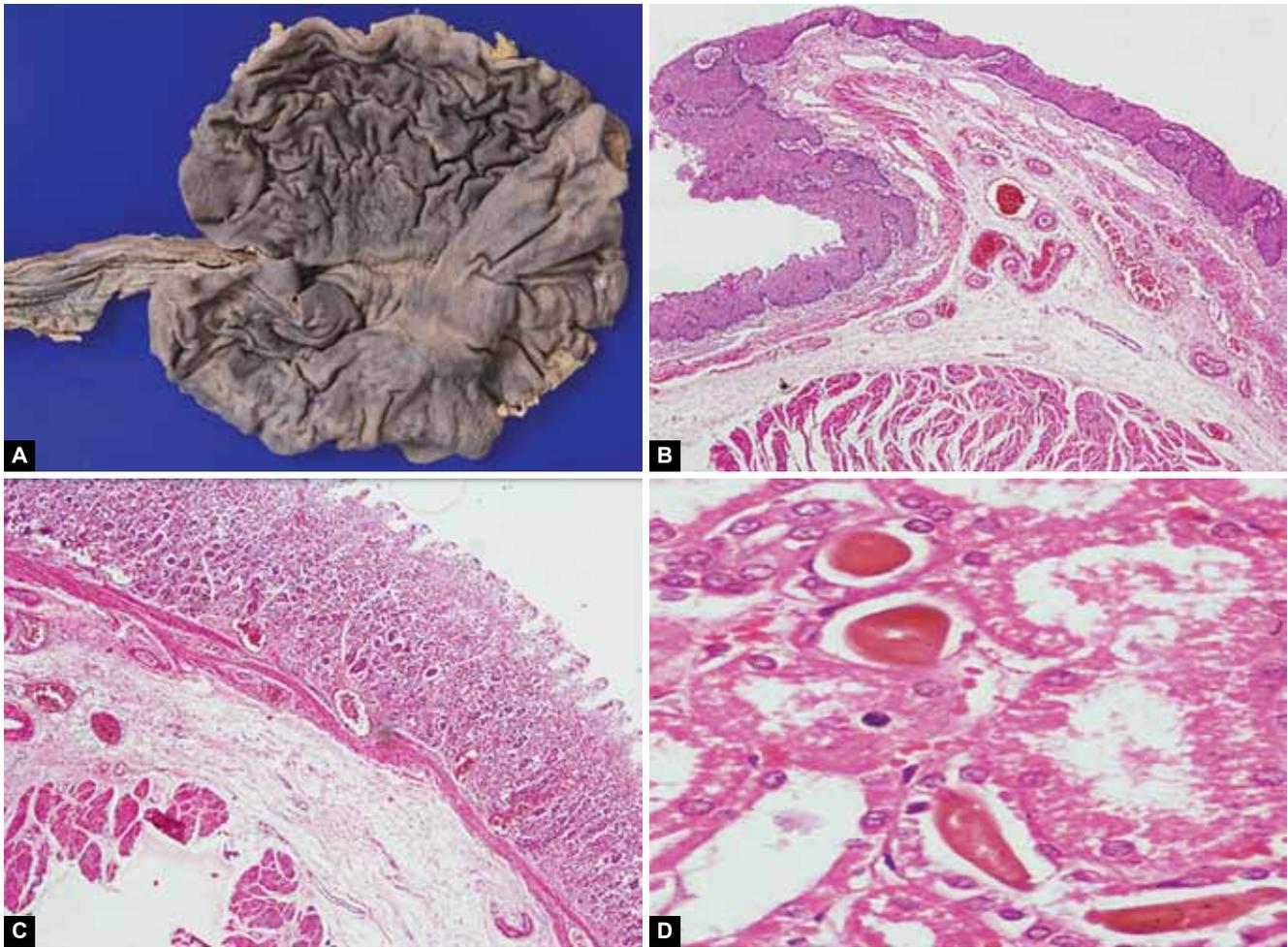
**Figs 2A to D:** Microphotographs of the liver: (A) Macrovesicular and microvesicular steatosis, (B) pseudoacinar transformation with cholestasis, (C) Mallory hyaline (arrow) (H&E 20 $\times$ ) and (D) pseudoacinar transformation and lymphomononuclear cells/histiocytic infiltrate (H&E 10 $\times$ )

etiology and pace of progression. The etiologies include viral infections, autoimmune conditions, drugs, metabolic causes including Wilson disease, etc. The criteria for defining acute liver failure are: (a) Evidence of liver dysfunction within 26 weeks of onset of symptoms, (b) uncorrectable coagulopathy with INR  $>1.5$  in patients with hepatic encephalopathy, INR  $>2.0$  in patients without encephalopathy and (c) no evidence of chronic liver disease either at presentation or in the past.<sup>3</sup>

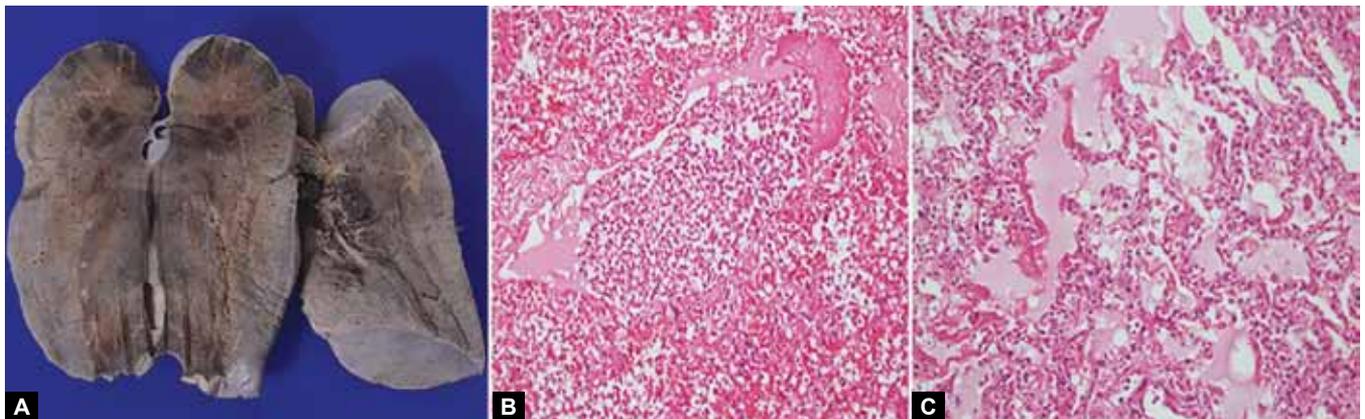
Wilson disease is a rare cause of acute liver failure which can present as fulminant hepatic failure or as an acute-on-chronic event. Wilson disease fulfills the criteria of acute liver failure, although in majority of cases chronic features are unrecognized. Liver fibrosis or even cirrhosis is not considered to be an exclusion criteria for categorizing patients as acute liver failure. Wilson disease is an autosomal recessive disorder characterized by accumulation of copper in liver, brain, kidney and cornea due to defective excretion. The WD gene, ATP7B, is located on chromosome 13q14.3 encodes a P-type ATPase. Although the failure to excrete biliary copper

is present from birth, clinical manifestations are rarely apparent before 5 years.<sup>4</sup>

Wilson disease is a great masquerader and its clinical presentation may be indistinguishable from other causes of acute and chronic hepatitis. A suspicion of acute Wilson disease is high in patients with deep jaundice, low hemoglobin, only mildly increased transaminases, and relatively low alkaline phosphatase. The presentation may be indistinguishable from other forms of chronic active hepatitis, with symptoms including jaundice, malaise, and vague abdominal complaints. The liver histology<sup>5</sup> in the setting of acute liver failure due to Wilson disease, shows marked hepatocellular degeneration and parenchymal collapse. A background of cirrhosis can be seen. Apoptosis of hepatocytes is a prominent feature. Lysosomal bound copper complexes can be detected in hepatocytes by stains like rhodanine and copper associated protein can be demonstrated by orcein stain. The detection of copper is highly variable by histochemical methods. In early stages of the disease, copper is mainly present in the cytoplasm bound to metallothionein and



**Figs 3A to D:** (A) Gross picture of mucosal surface of stomach and esophagus showing mucosal congestion. Varices seen in the (B) stomach, (C) esophagus (H&E 4x) and (D) kidney showing acute tubular necrosis and bile casts (H&E 40x)



**Figs 4A to C:** (A) Gross picture of cut surface of lung showing areas of hemorrhage, (B) microphotographs of the lung showing bronchopneumonia and (C) hyaline membranes with pulmonary edema

is not histochemically detectable. Also the amount of copper varies from nodule to nodule in the cirrhotic liver. The copper content in each cell is variable in the pre-cirrhotic stages.<sup>6</sup> In cases of confluent, multiacinar necrosis histochemical stains can be negative. The absence of histochemically identifiable copper does not exclude Wilson disease.

In the index case, the diagnosis of Wilson disease was made by the presence of very high serum bilirubin,

Coomb's negative hemolytic anemia, low serum ceruloplasmin and high urinary copper excretion. The liver histology showed multiacinar necrosis with macro and microvesicular steatosis. There was no evidence of cirrhosis in this case but fibrosis was present which could not be staged, as there was extensive necrosis. The presence of portal hypertension indicated by ascites, splenomegaly and varices points toward a chronic process, which is, however, not reflected in the histology. The orcein/

rhodanine stains and dry weight of copper were discordant as only few surviving hepatocytes were present.

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