Acute-on-chronic Liver Failure in a Young Girl

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An 11-year-old girl presented with progressive jaundice without cholestatic features for 2 months and progressively increasing abdominal distension for 10 days with irrelevant talk and inability to recognize parents for the last 1 day. There was a history of minor gum bleed and constipation for 3 days but no hematemesis or melena. There was no history of seizures, decreased urine output, fever or cough. There was no history of complimentary alternative medicine intake. In the past, she had Jaundice at the age of 2 years which resolved in 1 month. There was no history suggestive of autoimmune disease or liver disease in the family. She was immunized up to the age recommended by the National Immunization Scheme. She was treated with antibiotics before presentation to this institute, details of which were not available.

EXAMINATION

The child was pallor, icteric, and irritable E3V3M4; heart rate was 92 per minute; blood pressure was 128/80 mm of mercury; respiratory rate was 32 per minute; and the oxygen saturation was 92% on room air. Preabdominal examination revealed that the liver was 3 cm below costal margin, firm in consistency, with a span of 10 cm; spleen was 5 cm below left costal margin. There was free fluid in the abdomen. Central nervous system examined GCS-E₃V₃M₄, deep tendon reflexes were brisk, Plantar's were bilateral extensor. Other systems did not reveal any abnormality.

INVESTIGATIONS

	25.2.19 (outside PGI)	28.2.19	1.3.19	2.3.19
Hb mg/dL)	10.8	9.4	9.3	8.8
TLC (per mm ³)	10,000	8590	9100	6350
Platelets (per mm ³)	49,000	38,000	29,000	55,000
Bilirubin (mg/dL)	21.2/12.5	22.7/10.7	30.3	
AST/ALT (IU)	286/320	37/190		
ALP (IU)	312	244		
INR	4.23	5.08		
PT	56	84.6		
aPTT		99.9		
Serum urea (mg/dL)	14	19	12	17

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	25.2.19 (outside PGI)	28.2.19	1.3.19	2.3.19
Serum creatinine (mg/dL)	0.48	0.5	0.5	0.6
Serum Na/K (meq/L)	135/2.8	139/3.9	40/4.3	144/4.0

Arterial ammonia (28.2.19 and 1.3.19): 173 and 208 μmol/L

Ascitic fluid: 200 cells (all polymorphs), sugar 123, protein 0.3 g/L

Procalcitonin (2.3.19): 0.47

Blood C/S (28.2.19): sterile

HBsAg: Awaited

Anti-HCV: Nonreactive

Plasma Hb/urine Hb: 96/nil

DCT: Negative

Serum ceruloplasmin: Awaited

Autoimmune work-up: Awaited

USG abdomen (28.2.19): Liver, shrunken with heterogenous echotexture and multilobulated outline; spleen, 15 cm; PV, 9.5 mm at porta; GB, diffuse wall edema; moderate ascites and B/L pleural effusion; B/L kidneys, normal

COURSE AND MANAGEMENT

An 11-year-old developmentally normal, immunized for age girl, presented with a history of jaundice for 2 months, abdominal

distension for 10 days, and altered sensorium for 1 day. O/E she had pallor, icterus, asterixis, hepatosplenomegaly and free fluid per abdomen. Possibility of acute on chronic liver failure (ACLF) vs acute liver failure (ALF) was kept. In view of signs of raised intracranial tension (ICT), she was started on intracranial pressure (ICP) lowering and anti-hepatic encephalopathy (HE) measures including 3% saline, lactulose and rifaximin. She was intubated at 18 hours of admission in view of poor Glasgow coma scale. In view of deranged coagulogram with gum bleed, fresh frozen plasma was transfused. She had a worsening respiratory failure with profuse bleed from the endotracheal tube. X-ray of the chest showed bilateral diffuse homogeneous opacities possibly due to pulmonary hemorrhage. She suffered cardiorespiratory arrest on day 3 of hospital stay. Cardiopulmonary resuscitation was done according to the protocol but she could not be revived.

- Units diagnosis ALFACLF
- Hepatic encephalopathy, ascites, coagulopathy
- Pulmonary hemorrhage

CASE DESCRIPTION

In this 11-year-old developmentally normal, immunized for age girl with a history of self-limiting jaundice at 2 years of age now presented with non-cholestatic, progressive jaundice 2 months with thrombocytopenia, mixed hyperbilirubinemia, transaminitis 6–8× upper limit of normal, hypoalbuminemia, coagulopathy, shrunken liver with splenomegaly, low protein ascites (10 days) with spontaneous bacterial peritonitis and altered sensorium since 1 day.

With this background the child falls into which syndromic diagnosis?

Following are the definitions of each syndromic diagnosis:

Acute Liver Failure

Jaundice with coagulopathy (INR >1.5) and any degree of encephalopathy within 26 weeks without preexisting liver disease (exceptions: Wilsons, AIH, BCS, vertically acquired CHB).

Acute-on-chronic Liver Failure

Jaundice (serum bilirubin >5 mg/dL) and coagulopathy (INR>1.5) complicated within 4 weeks by clinical ascites and/or encephalopathy with previously diagnosed or undiagnosed chronic liver disease/cirrhosis.

Subacute Hepatic Failure

Progressive or persistent jaundice with unequivocal ascites developing >4 weeks after onset of jaundice with evidence of ongoing necrosis; baseline liver normal.

The index case will fall in ACLF >> SAHF >> ALF (subacute type).

Because of the typical presentation of jaundice followed by ascites and/or HE, with shrunken liver, splenomegaly, thrombocytopenia will favor more ACLF than others.

The etiology that favors ACLF is

- Acute: acute viral hepatitis, flare of underlying chronic disease
- Chronic: autoimmune hepatitis, Wilsons

SAHF is acute viral hepatitis, autoimmune hepatitis

Acute liver failure is acute viral hepatitis, autoimmune hepatitis, Wilsons

According to the Indian data of pediatric ALF, the commonest etiology is viral infections followed by metabolic liver diseases and drug induced liver injury.

In pediatric ACLF, Wilsons and AIH are the commonest chronic etiologies while acute viral hepatitis is the commonest precipitating event.

For SAHF limited data was available, commonest etiology is acute viral hepatitis (HEV and HAV) followed by autoimmune hepatitis and drug-induced liver injury (DILI).

Final Diagnosis

- ACLF (SAHF, subacute ALF)
- Acute
 - Acute viral hepatitis (HEV)
 - Flare of AIH/Wilsons
- Chronic
 - AIH
 - Wilsons
- Ascites, hepatic encephalopathy, coagulopathy
- SBP

Cause of death: pulmonary hemorrhage

CLINICAL DISCUSSION

Chairperson (Prof Rakesh Kochhar): Thank you Arke. Nicely elaborated the case. Please join me here. Now case is open for comments and opinion.

ProfDr RK Dhiman: Clinical presentation of this case is more like ACLF and meets current criteria for the same. Patient had some history of jaundice at 2 years and recovered, indicating some underlying liver disease from 2 years of age and now present with acute manifestation. The possibilities of Wilson and autoimmune are considered in this setting as discussed by Dr Arke. Whatever may be, at present this patient has to be managed as per ALF protocol.

ProfDr Usha Dutta: I also go with possibilities of Wilson and autoimmune hepatitis. If we have serum markers, it would have helped in sorting out the differential diagnosis.

ProfDr Virender Singh: The clinical picture is not matching the criteria for ACLF. Definitely we are dealing with some chronic liver disease.

ProfDr Sanjay: In ultrasound, it was mentioned as shrunken liver and on clinical examination, liver was palpable. There was some clinic radiological discordance. Is it really chronic?

Chairperson (Prof Rakesh Kochhar): Various opinion from the house. We will see what will be there in autopsy. May I request Dr Aravind to show autopsy findings.

Pathology Findings (PM)

A partial autopsy was performed. The prosecutors noted the peritoneal cavity was filled with a straw color fluid and yielded 250 mL of fluid. The pleural and peritoneal fluids were within normal limits.

Liver: Weight 365 g; capsule was wrinkled and relatively shrunken; firm in consistency; cut surface showed irregular pale to tan colored areas of variable size alternating with greenish yellow nodules of variable size. Few nodules are seen on the surface measuring 3.5 cm in maximum dimension. Biliary tract did not show structural abnormality. Portal vein did not show any thrombus Figures 1A and B.

Microscopic examinations revealed large areas of necrosis with preserved islands of hepatocytes in-between. Necrosis was pan lobular and nonzonal in distribution. Most of the portal tract

Figs 1A to R: (A and B) Cut surface of liver shows irregular pale to tan colored areas of variable size alternating with greenish yellow nodules of variable size. Few nodules are seen on the inferior surface measuring 3.5 cm in the maximal dimension (gross photograph); (C and D) Multiacinar panlobular necrosis with preserved island of hepatocytes (100 $\times$, microphotograph, H&E); (E) Centrilobular necrosis with loss of hepatocyte around central venule (200 $\times$, microphotograph, H&E); (F and G) Central venulitis with lifting of endothelial cells by inflammatory cells (400 $\times$, microphotograph, H&E); (H and I) Moderate lymphoplasmacytic inflammatory cell infiltrate in portal tracts with interface hepatitis rich in plasma cells (200 $\times$ and 400 $\times$, microphotograph, H&E); (J) Few hepatocytes in periportal region show emperipolesis (200 $\times$, microphotograph, H&E); (K and L) Masson trichrome and orcein stain highlight portal tract fibrosis with extension of fibrous septae into hepatic lobules and few portoportal bridging fibrosis indicating chronicity (200 $\times$, microphotograph); (M and N) Extensive bile ductular proliferation seen adjacent to necrosis (200 $\times$, microphotograph, H&E and CK 7 immunostaining); (O and P) Microphotographs of lymph node show increase in number of histiocytes with hemophagocytosis (200 $\times$, microphotograph, H&E and MT); (Q and R) Cut surface of lungs shows hemorrhagic consolidation and corresponding section shows hemorrhage in alveolar spaces (100 $\times$, microphotograph, H&E)

showed moderate lymphomononuclear cell inflammation rich in plasma cells. Porto-portal and occasional Porto-central fibrosis was seen on orcein stain. However, no cirrhotic nodules were present. Significant interface hepatitis was seen. Emperipolesis and hepatocyte rosettes were also present. Both central vein and portal vein showed venulitis. Extensive bile ductular proliferation was noted highlighted by CK7 stain. No significant cholestasis or steatosis was present. No storage cells were seen. Rhodamine stain did not highlight any copper deposits Figures 1C to N.

Spleen: Weight 273 g, enlarged and congested. Sections examined showed expansion of red pulp with capillarization of sinusoids. Focally hemophagolymphohistiocytosis was seen.

Lymph nodes were enlarged in peripancreatic region and para-aortic region and on microscopy showed reactive germinal center with prominence of histiocytes with hemophagolymphohistiocytosis Figures 1O and P.

Kidneys: weight 245 g; cut surface was unremarkable. On microscopy, all four compartments did not show any diagnostic change.

Heart: Weight 157 g; both grossly and microscopically unremarkable.

GIT: GE junction showed dilated veins both in lamina propria and submucosal layer.

Small intestine and large intestine were grossly and microscopically normal.

Lungs: Weight 768 g. Pleuron was dull. Pleural tags were seen. Cut surface was consolidated to feel and showed hemorrhages in all the lobes of right and left lung. On microscopy, alveolar spaces were filled with hemorrhage. Fibrin was noted along alveolar ducts and respiratory bronchioles Figures 1Q and R.

Adrenals, thyroid, skin, uterus, ovaries, and skeletal muscle did not reveal any significant pathological findings.

Bone marrow showed mildly hypocellular marrow with evidence of hemophagocytosis.

Final Autopsy Diagnosis (PM 29377): A 11-year-old girl who presented with ACLF.

- Massive panlobular centrilobular hemorrhagic necrosis with chronic hepatitis (Score 4) (typical of acute exacerbation of chronic autoimmune hepatitis).
- Portal hypertension: ascites, splenomegaly and esophageal varices.

- Hemophagolymphohistiocytosis in lymph nodes, spleen and bone marrow.
- Pulmonary hemorrhages.

FINAL DISCUSSION

Prof Rakesh Kochhar: Thank you, Dr Aravind. Please join me here.

Prof Dr RK Dhiman: I think Dr Arke has microscopic eyes, he analysed the diagnosis exactly.

Prof Ashim Das: This is a classical finding of acute exacerbation of chronic autoimmune hepatitis. Massive multiacinar, pan lobular necrosis along with predominant centrilobular necrosis is described in autoimmune hepatitis. Central venulitis with lifting up of endothelial cells as shown is typically described in autoimmune hepatitis.

Prof Dr Sadhana Lal: Extensive Liver progenitor cells mediated bile ductular proliferation seen in response to massive hepatic necrosis would result in regenerative nodule but cannot compensate the loss.

Dr Aravind: Probably these regenerative nodules might be the reason for palpable liver on examination although shrunken liver was described on ultrasonogram.

Prof Dr Usha Dutta: Massive hepatic necrosis is shown in autopsy. Is there any chronicity?

Prof Dr Ashim Das: Yes, there are fibrous septae with extension into hepatic lobule with porto-portal and occasional portal central bridging fibrosis. Definitely there is chronicity.

Prof Rakesh Kochhar: Thank you all. We had a good clinico-pathological case discussion and demonstration of acute exacerbation of autoimmune hepatitis today.

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