Clinicopathological Conference Report

A Three-month-old Female Child with Acute-on-chronic Liver Disease: How Far We reached after Autopsy?

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Pathology Senior Resident: Dr Aravind Sekar
DOA: 23.7.16
DOD: 6.8.16
Date of CPC: 23.11.2016

Admitted under Pediatric Gastroenterology Services. Clinician in-charge: Prof BR Thapa

CHIEF COMPLAINTS

A three-month-old child admitted with chief complaints of yellowish discoloration of body for 3 days, black tarry stool for 2 days, vomiting of blood for 1 day.

HISTORY OF PRESENT ILLNESS (RECONFIRMED FROM PARENTS TELEPHONICALLY)

Child was well 5 days prior to admission. She was noted to have a yellowish discoloration of body and bright colored urine after second dose of vaccination. Subsequently, she passed two to three scanty, black tarry stools; one episode of dark altered blood vomitus; developed lethargy and poor feeding. No history of acholic stools, odd body odor, skin bleeds, fever, rash, diarrhea, abdominal distention, tachypnea, seizures.

PERINATAL/BIRTH HISTORY

No history of antenatal jaundice, hyperemesis, hypertension, fever, rash, vaginal discharge. Born at term by normal vaginal delivery; no asphyxia; birth weight—2 kg [term intrauterine growth response (IUGR)]; smooth perinatal transition; no neonatal jaundice; no feed intolerance. Immunization was delayed due to low birth weight (LBW).

FAMILY HISTORY

Born to nonconsanguineous couple. No history of similar illness. First child is too young and normal.

DEVELOPMENTAL HISTORY

Appropriate for age.

IMMUNIZATION HISTORY

Immunized for age as per National Immunization Schedule (Bacillus Calmette-Guérin and two doses of Diphtheria, Pertussis, Tetanus/oral polio vaccine/hepatitis B).

FEEDING HISTORY

Breast-feed supplemented by diluted, sugared, cow’s milk, since birth.

GENERAL PHYSICAL EXAMINATION

Patient was afebrile with heart rate of 90/minute, respiratory rate—22/minute maintaining oxygen saturation at SPO₂—98% (room air). Oral mucosal bleed was noted. Anterior Fontanelle measured 1 × 1 cm and was not bulging; Final Physiologic Classification: Systemic dysfunction; Triage Classification: Level 4 (less urgent); weight: 3.0 kg (<−3 Z-score); Occipital-frontal circumference: 33.5 cm (<−3 Z-score).

On examination, she had pallor, edema, icterus. There was no cyanosis, lymphadenopathy, clubbing. There was no dysmorphism, coarse features, or specific odor.

On systemic examination, abdomen was soft, nontender, distended with central, everted umbilicus. Fluid thrill was present. On palpation, liver was irregular, firm,
A Three-month-old Female Child with Acute-on-chronic Liver Disease

On evaluation of central nervous system (CNS), she was conscious and alert, oriented to mother, fixing, and following light. There were no cranial nerve deficit or no meningeal irritability. Motor, sensory, and cerebellar senses were normal. On examination of chest and central vascular system (CVS), S₁ and S₂ were murmur. Trachea was central with resonant note. There was no added sound.

INVESTIGATIONS

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<td>Platelets</td>
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**Table 1:**

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<td>Bilirubin</td>
<td>2 mg%</td>
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- **Lipid profile:** Triglyceride—97.3; cholesterol—231; low-density lipoprotein—75; high-density lipoprotein—136.5
- **Direct Coomb’s test (DCT) and glucose 6 phosphate deficiency (G6PD):** Not available
- **Eye:** Slit Lamp and Fundus: No cataract, choroidal-retinal synaechae, retinal abnormal (ABN)
- **Ultrasonography (USG) abdomen (ABD):** 25/7/16: liver 6.9 cm; normal outline and echotexture; hepatic vein (HV) and portal vein (PV) normal; spleen: 6.3 cm; pancreas: N size and increased echogenicity; moderate ascites
- **Urine red subs:** Nil
- **Blood/Urine C/S:** Sterile
- **VBG low HCO₃⁻:** Metabolic acidosis; normal lactate
- **TMS/GCMS (Received PM):** Normal; carnitine/acyl carnitine profile: N
- **GALT Assay/urine succinyl acetone assay:** Could not be done

**Course and Management**

Diagnosed to have ALF with hepatosplenomegaly, coagulopathy, systolic blood pressure (SBP), gastrointestinal (GI) bleed, and sepsis. Etiology was considered probably metabolic liver disease and started on cefotaxime, octreotide, pantoprazole. Additionally was supported with plasma red blood cells fresh frozen plasma, vitamin K. Albumin infusion was given twice along with fat and water soluble vitamin supplements. Gastrointestinal bleed was passive after admission. In view of worsening
counts, antibiotics were upgraded to vancomycin/imipenem. Milk was stopped presuming galactosemia on day 2; however, there was no improvement in coagulopathy/ascites. Hemoglobin dropped in absence of GI bleed, and packed red blood cells were repeated twice. Urine output remained normal and SBP resolved. Ascitic fluid was tapped almost daily due to rapid refilling. Child was stable and active, alert till 2 am when she fed normally. History of decreased feed intake at 4.30 am; subsequently found unresponsive at 6 am by Junior Resident on 6/8/2016. Milk aspiration was suspected; resuscitation was done; however, child could not be revived.

DISCUSSION

Based on data and investigations available, we were dealing with a very young infant with LBW and poor weight gain after birth with liver failure and strikingly difficult to manage ascites: Whether it is acute liver failure (ALF) or acute-on-chronic liver failure is a matter of semantics, the etiology being similar at this age. Diagnostic possibilities in a young infant are as follows:

Infections

<table>
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<tr>
<th>Infections</th>
<th>Hematologic Ds</th>
<th>Vascular</th>
<th>Metabolic</th>
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<td>• HSV</td>
<td>• HLH</td>
<td>• HVOTO/</td>
<td>• Toxic metab</td>
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<tr>
<td>• Echovirus</td>
<td>• Cong. leukemia</td>
<td>• BCS</td>
<td>• Energy defects</td>
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<tr>
<td>• Adenovirus</td>
<td>• Hepatitis B, E</td>
<td>• CHF</td>
<td>• Complex molecules</td>
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<tr>
<td>• Parvovirus</td>
<td>• Severe sepsis</td>
<td></td>
<td></td>
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<tr>
<td>• Others</td>
<td>• Neonatal Hepochromatosis</td>
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Of these, hematological cause was safely ruled out; complete hemogram and blood picture were not supportive.

Regarding infectious etiology, bacterial infections are unlikely as they present with cholestasis rather than liver failure. Hepatitis B and E can present with ALF in babies but will not be considered because of negative maternal history. The delayed presentation in the absence of skin lesions and other stigmata virtually rules out herpes. Parvovirus B19 usually presents with severe hepatitis, ascites, liver failure, anemia; however, unlike this case OT/PT are low. Paramyxovirus presents with syncytial giant cell hepatitis, moderate increase in OT/PT, severe cholestatic hepatitis and cirrhosis by 1 year not ALF; echovirus/Coksackie/adenovirus can present with severe hepatitis, ALF, marked increase in OT/PT; however, there is nothing pathognomonic on histopath-polymerase chain reaction being diagnostic.

Coming to vascular causes like hepatic venous outflow obstruction/Budd–Chiari syndrome/veno occlusive disease, these are rare in early infancy but worth consideration in any baby with intractable ascites; a marked increase in OT/PT; severe jaundice and coagulopathy, due to hepatic venous outflow tract obstruction (HVOTO) is more common in infants, but low serum-ascites albumin gradient (SAAG) ascites and prolongation of liver failure would be unusual; moreover, the USG and Doppler were not suggestive and the setting in which HVOTO occurs in infants, i.e., neoplasia, venous catheters, hypercoagulable states, chemotherapy for hematological malignancies, congestive heart failure, etc. were missing; hence, it is an unlikely possibility.

Metabolic liver diseases can account for up to 40% of ALF in infants. Type I disorders due to accumulation of toxic metabolites need exposure to the precursor via feeding, do not affect the fetus, baby being normal at birth. The deterioration occurs after birth in an acute or subacute manner, after a symptom-free period. Galactosemia, tyrosinemia I, hereditary fructose intolerance (HFI) are the likely candidates. The lack of encephalopathy, skin changes, and peculiar odor/dysmorphism almost ruling out organic acidemias, mevalonic aciduria, urea cycle defects, porphyrias. The type II IEM result from defective energy production or utilization at the level of the respiratory chain/cytoplasm. Intrauterine growth rate due to prenatal onset is very possible as is an ALF-like presentation in neonatal period/early infancy; mitochondrial hepatopathy is a distinct possibility among type II ds; Transaldolase being unlikely because of phenotype as also are the glycogen storages, due to the presentation. The type III IEMs due to accumulation of complex molecules are a rare cause of liver failure due to organelle dysfunction, e.g., peroxisomes; however, they have impressive visceromegaly and characteristic coarse features/neurologic involvement, thereby ruling out disorders like Zellweger’s, congenital defects of glycosylation, Wolman’s disease, etc. Niemann Pick Type III can have a varied timeframe of other systemic involvement and can be kept in the D/D of liver dysfunction with ascites in young infants. Thus at this point of time in this baby one could, besides galactosemia, tyrosenemia, and HFI, also discuss the possibilities of mitochondrial hepatopathies, fatty acid oxidation disorders (FAODs), neonatal hemochromatosis, Niemann Pick C, and bile acid synthetic defects (BASDs).

Generally, BASD is cholestatic liver disease with fat malabsorption; However, Δ4-3-oxysteroid 5β-reductase deficiency can present with severe cholestasis and liver failure. Abnormal bile canaliculi in a focal mosaic pattern is noted. Fast atom bombardment spectroscopy of urine for abnormal metabolites is diagnostic. The diagnosis cannot be proved on histology alone. It is a rare disorder and looks unlikely.

Galactosemia is an androgen receptor disorder due to deficiency of galactose-1-phosphatase uridyl transferase/epimerase and presents with acute/subacute/
chronic cholestasis/with liver failure/cirrhosis; cataract is present only in 50%. However, LBW is unusual as it is the very marked elevation of aspartate transaminase (AST)/alanine transaminase (ALT) and lack of any improvement in INR/albumin and ascites despite 2 weeks off milk. Histology can show cirrhosis but is nonspecific and only GALT assay can clinch the diagnosis. Hence, it is a difficult diagnosis to prove.

Tyrosenemia is due to fumarylacetoacetase deficiency which causes accumulation of hepatotoxic maleylacetate and fumarylacetoacetate succinylacetone. It can present with liver failure in 1 to 6 months with coagulopathy, ascites, and jaundice. However, unlike this case, bilirubin is usually well below 10 mg% and AST/ALT are only mildly elevated; rickets may develop later; marked elevation of alpha fetoprotein is the norm; diagnosis needs urinary succinylacetone/mutation analysis; histology will show cirrhosis/regenerative nodules/cholestasis/hemosiderosis—again nonspecific findings in a baby with cholestasis and liver failure; possible with reservations but difficult to prove.

Hereditary fructose intolerance is due to deficiency of aldolase B in liver, intestine, and kidney, and caused by accumulation of toxic fructose 1 phosphate in these tissues, and cause liver and renal dysfunction. The baby was exposed to sucrose, so possible but features which do not fit in with our case is the absence of features of intolerance; there was no diarrhea/vomiting/distention; the striking ascites is also unusual; diagnosis is by enzyme assay in liver tissue/genetic analysis/EM may give a clue; again a difficult diagnosis to make on histopath alone.

Primary mitochondrial hepatopathy unless looked for can be a missed cause for liver failure of early infancy. Multisystem disease may not always occur at presentation due to heterogeneous expression of genetic defect in different tissues; IUGR/ALF/moderate to marked rise of AST/ALT as in this case is well described; for various respiratory chain complex enzyme defects—single/multiple/mitochondrial DNA depletion syndromes, e.g., POLG/DOGOK. Diagnosis needs EM/muscle biopsy; likely in these patients.

Usually, FAODs do not present in early infancy; CNS and CVS manifestations predominate the clinical picture and liver involvement is usually unimpressive, AST/ALT being only mildly elevated; also our case had a normal acyl carnitine/carnitine profile during the decompensated state and no documentation of fatty liver on USG. So, this looks unlikely.

Neonatal hemochromatosis is an alloimmune gestational disease, in which maternal immunoglobulin G causes complement-dependent severe fetal liver injury and dysregulated handling of iron by the fetal liver, causing abnormal iron distribution in the body; an important cause of neonatal liver failure with LBW, though rarely presented, may be delayed as in index case; however, AST/ALT are mildly elevated; pancreas may be hyperechoic on imaging (as in this case); hemolytic anemia may also occur. However, liver echotexture was normal on USG—which is odd. Unfortunately, we do not have S. ferritin/buccal biopsy available, which could have helped us.

Niemann Pick C disease, a disorder of abnormal intracellular cholesterol trafficking, presents with prolonged cholestasis with ascites, <10% of this rare disease progresses to liver failure by 6 months; thus, this seems an unlikely diagnosis.

The riddle in this case is: What is the (1) cause of the severe hemolysis? immune-mediated?, (2) cause of death: Dyselectrolytemia/arrhythmia?

So what is my possibility in this term, IUGR with failure to thrive/ALF and difficult to manage ascites/markedly elevated AST/ALT with ratio >4!/unexplained hemolysis/significant >50% unconjugated hyperbili- rubinemia and a hyperechoic pancreas and a sudden death?? The shortlist will include: (1) Mitochondrial hepatopathy; (2) neonatal hemochromatosis; (3) tyrosinemia/HFI.

CLINICAL DISCUSSION

Prof S Varma: Thanks Dr Sadhna. Difficult to discuss case but you seemed to have done it very meticulously. Comments from treating unit please.

Dr Jagdeesh M (Senior Resident): Metabolic and infec-

Prof Meenu Singh: Main growth retardation indicator is

Dr Thapa: This baby was gaining 10 gm weight per
day, may be due to ascites but this weight gain is appa-

Prof Meenu Singh: Main growth retardation indicator is

JPMER
be considered in this case is cystic fibrosis, it can present as ALF, but point against is splenomegaly, which is indicating further this child suffered from one of storage disorder. HFI and mitochondrial hepatopathy may be etiology, as child was exposed to top feed.

*Dr Renu Suthar (Paed. Neurologist):* This presentation is consistent with mitochondrial disorders, especially mitochondrial DNA depletion syndromes like POLG.

*Prof Sanjay Jain:* Child had hyperkalemia. One important cause is acute hemolysis. Combining hypernatremia, hyperkalemia, adrenal, liver failure and hemolysis in this case, I do not know the etiology autoimmune disease should be considered.

*Dr Sadhna Lal:* The baby did have failure to thrive. As far as cystic fibrosis is concerned, it causes a focal segment involvement of liver and cholestasis. Liver failure is due to cirrhosis and does not occur before the second decade.

*Prof Subhash Varma:* Dr Kirti Gupta is the right person to be called now and let see what this young patient had.

**PATHOLOGY PROTOCOL**

Partial autopsy was done in this case; externally, prosecutor noted pallor with icterus. Serous cavities: Yielded 500 mL (icteric fluid) in peritoneal cavity, 50 mL of serous fluid in pleural cavities, 15 mL of serous fluid in pericardial cavity.

**Liver**

Weight: 105 gm gross. Capsular and cut surface smooth with tiny nodules (<3 mm), cut surface was bile stained (Fig. 1A). Microscopy revealed distorted architecture with porta-portal and porta-central bridging. Portal tracts are replaced by fibrous bands which are extending to the peri-portal areas with fibrosis also noted in perivenular zones (Figs 1B to D). Significant pericellular fibrosis is identified. Focal peri-portal cholangiolar proliferation is noted (Fig. 1E). Hepatocytes show pseudoacinar transformation, with micro- and macrovesicular steatosis and prominent giant cell transformation (Figs 1G and H). Intrahepatocytic and cholangiolar cholestasis is noted along with extramedullary hematopoiesis (Figs 1I to L). Hemosiderosis is present as well. CK7 immunostains (Fig. 1F) highlights the neo-cholangioles and ductular metaplasia of hepatocytes. No macroregenerative nodules seen. Extrahepatic biliary tract is within normal limits.

Pancreas was grossly normal and showed islet cell hyperplasia.

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![Figs 1A to D](image_url)

**Figs 1A to D:** (A) Capsular and cut surface smooth with tiny nodules (<3 mm), cut surface is bile stained (gross photograph); (B to D) portal tracts are replaced by fibrous bands which are extending to the periportal areas; fibrosis is also noted in perivenular zones; (B) H&E, 200× magnification; (C) reticulin stain, 200× magnification; (D) masson trichrome stain, 200× magnification
A Three-month-old Female Child with Acute-on-chronic Liver Disease

Figs 1E to L: (E) Focal periportal cholangiolar proliferation; (F) intrahepatocytic and cholangiolar cholestasis (E, F, H&E), 400× magnification; (G) CK7 immunostains highlight bile duct proliferation; (H) hepatocytes show pseudo-acinar transformation, with micro- and macrovesicular steatosis and prominent giant cell transformation (H&E, 400× magnification); (I) Fouchet stain highlights cholestasis (400× magnification); (J) Perl’s stain highlights hemosiderosis (400× magnification); (K, L) extramedullary hematopoiesis (H&E, 400× magnification)
Lungs

Weight: 70 gm. On gross examination were subcrepitant with focal areas of congestion. Trachea and airways did not show inspissated secretions. Micro: Occasional secondary bronchiole showed secretions, foamy macrophages identified in most of the alveoli (Fig. 2A). Cytomegalovirus (CMV) inclusions were identified in pneumocytes lining the alveoli (Fig. 2B) focally. Many pigment laden macrophages were noted as well. No fungal hyphae/abscesses were seen.

Heart

Weight: 20 gm. All chambers and valves were within normal limits. A single 8 mm abscess noted in left ventricular wall (Fig. 3A), which microscopically is composed of central necrotic material admixed with neutrophils and giant cells (Fig. 3B) and few *Aspergillus hyphae* (Figs 3C and D).

Spleen

Weight: 40 gm. Gross and microscopically within normal limits.

Lymph Nodes

Small peripancreatic region and omental LNs (0.6–0.8 cm) identified. Adequate representation T and B lymphocytes.
A Three-month-old Female Child with Acute-on-chronic Liver Disease

seen on CD3 and CD20, one of the LNs is filled with hemosiderin laden macrophages. Lymphoid aggregates in appendix and Peyer’s patches adequate.

Thymus
Weight: 2 gm. Within normal limits. Microscopic examination showed stress-induced involution with excess of Hassall’s corpuscles. Adequate representation of CD3+ T lymphocytes. Bone marrow was within normal limits.

Kidneys
Weight: 50 gm; Gross examination on capsular surface showed fetal lobulations. Glomeruli, tubules, and interstitial compartments within normal limits. Occasional tubular dilatations, bile casts, and crystals noted.

Adrenals
Weight: 1 gm. Gross and microscopic examination was within normal limits; Small, large intestine, stomach, esophagus did not show any diagnostic abnormality. Uterus was within normal limits.

Autopsy Diagnosis
- Micronodular cirrhosis (consistent with galactosemia) with portal hypertension (ascites and splenomegaly)
- Myocardial abscess (fungal, aspergillus): Left ventricle
- The CMV inclusions and foamy macrophages (milk globules) in lungs
- Islet cell hyperplasia.

FINAL DISCUSSION
Prof Thapa: We have to learn infantile liver. There are enough evidence that metabolic cause is ALF in this case. Galactosemia is the most common one we encounter in infants. Though it presents shortly after birth, there is dureate variant which can present later. Triggering event is probably sepsis. Only caveat in this case, enzyme levels are not known and whether accompanied G6PD deficiency coexists with it, which remain unanswered. Bleeding could be because of coagulopathy.

Prof Meenu Singh: Whether CMV infection is localized or generalized? Because CMV was seen only in lung, not in other organs, can we label as CMV disease? Second, although histopathological features are suggestive of galactosemia, we definitely need GALT assay and type of mutation in this case to confirm.

Dr Kirti Gupta: Some hepatocyte loss is noted, though it was largely fibroed and cirrhotic.

Dr Sadhana Lal: I think the histology shown is largely nonspecific and common to galactosemia/tyrosinemia/HFI/mitochondrial disease. There is nothing pathognomonic. Without enzyme assay/genetic mutation study and electron microscopy, one cannot narrow down to any particular diagnosis.

Prof Kim Vaiphei: For demonstrating CMV inclusions in liver, ideally immunohistochemistry should be done.

Prof Ashim Das: This liver histology and 3-month-old child, out of three disorders, galactosemia is most likely. Tyrosinemia and HFI are unlikely with this histology.

Prof Yashpal: Patient had myocardial abscess; it might cause for increase in SGOT/SGPT secondary to heart failure.

Dr Sadhana Lal: A major argument against galactosemia is that there was no improvement in ascites/coagulopathy despite nearly 15 days of a lactose-free diet; hence, I am not sure that we have ruled out other possibilities.

Prof Subash Varma: Toward the end CMV infection, myocardial abscess apart from metabolic disorder together made the clinical situation complex. Even now clear explanation for very high SGOT/SGPT is not available.

Thank you all for participating in the CPC and we wish for more audience in next session.

COMMENTARY
This case presented with cirrhotic liver by the age of 3 months with superadded rise of liver enzymes complicating the clinical scenario. Most likely cause of cirrhosis at this age with micronodular cirrhosis and absence of iron would be galactosemia; however, clinically no improvement on withdrawal of lactose difficult to accept this as the final diagnosis. Enzyme studies is the only answer for such analysis. During life many other cofactors contribute to the complexity of the disease, hence, difficulty in diagnosis.

SUGGESTED READINGS