

Clinicopathological Conference Report

I am still Around

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This case was discussed on 2nd Nov 2011 as a staff clinicopathological exercise at Postgraduate Institute of Medical Education and Research, Chandigarh, India

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Clinical Protocol

A one-year-old girl (resident of Bhatinda, Punjab) was first admitted at PGIMER under pediatric hematology-oncology at the advanced pediatric center on 05.10.2011 with complaints of fever and progressive abdominal distension for 1 and a half months. Fever was intermittent, associated with occasional vomiting and documented up to 101°F. Vomiting was nonbilious and nonprojectile. She also had progressive pallor for 1 month, which was not initially associated with jaundice, edema or bleeding manifestations. She reported weight loss of 500 gm over 10 days. Patient was worked up for the possibility of hemolytic anemia and storage disorder and discharged on 08.10.2011. She received one unit packed red cell transfusion on 12.10.2011, following the bone-marrow, done on OPD basis. She was readmitted at PGIMER on 20.10.2011 in pediatric emergency for the same complaints, with new onset cough and coryza for 7 days and fever with respiratory difficulty for 5 days. She was born through nonconsanguineous marriage, at term and weighed 1500 gm at birth. There was no birth asphyxia and her development milestones were appropriate for age. Her two elder siblings, both girls are asymptomatic. There was no apparent history of contact with tuberculosis patient.

Examination

At first admission: Afebrile, Pulse-130/minutes, rest of the vital parameters normal. Weight-7 Kg (<3rd centile), length-67 cm (<3rd centile), head circumference-42 cm ($\leq 2SD$). She had pallor, generalized lymphadenopathy, a cutaneous hemangioma measuring 1 × 0.5 cm, at right mandibular area (since birth), and right eye convergent squint (since birth). No petechiae, icterus, edema, cyanosis, clubbing, facial dysmorphism or cataract was seen. Systemic examination revealed hepatomegaly (liver span 9 cm, firm, sharp margin, smooth surface), splenomegaly (8 cm below left costal margin, firm). Ejection systolic murmur was heard all over the precordium (best at tricuspid area). The central nervous system examination was normal.

At second admission: In addition, she had tachypnea, retractions with bilateral crepitations, pallor, icterus, pedal edema, hepatosplenomegaly with ascites.

Investigations

	20.09.11 outside	07.10.11 1st admission	20.10.11 2nd admission	21.10.11
HB	5.7	6.0	7.9	8.3
TLC	9700	15300	12300	19200
DLC	L54	N55L38M5E2	—	—
Platelets	2.5 lac	218×10^3	137×10^3	—
Retic count	1.2	—	—	—

Peripheral blood film: Microcytic hypochromic, anisopoikilocytosis, few target cells and elliptocytes. No malarial parasite seen.

ABG

	20.09.11 outside	21.10.11 2nd admission
<i>Biochemistry</i>		
SGOT	—	506
SGPT	305	212
ALP	—	181
S Bil	0.95	4.5
S Prot/Alb	—	5.5/2.0
Ca	—	8.0
Urea	—	51
Creatinine	—	0.2
Na ⁺	—	145
K ⁺	—	4.5
Cl ⁻	—	114
RBS	—	67 mg/dl
<i>Coagulogram</i>		
PT	—	30 (14 sec)
PTI	—	46%
APPT	—	66 (25-35 sec)
CRP	—	NR

	06.10.11	20.10.11 (Admission)	21.10.11
pH	7.46	7.39	7.1
PO ₂	78	83	42.8
PCO ₂	28.1	37	49.9
HCO ₃	19.6	23	15.1
BE	- 2.7	- 2.2	- 14.6
SO ₂	96%	96%	55.6%

Hemoglobin electrophoresis: Normal (Hb A 95/A₂ 2.4/F 2.7).

Bone marrow: Normocellular marrow spaces with adequate representation of all three hematopoietic elements. No storage cells. Low iron stores.

HIV serology: Nonreactive.

USG abdomen: (Outside-20/09/11)-Liver-10.4 cm, normal echotexture. GB distended normally. PV-normal calibre. Spleen 9.6 cm normal echotexture and no focal lesion. At PGIMER- Hepatosplenomegaly with mild ascites.

Ascitic fluid: 500 ml aspirated. No WBC.

Sugar/protein: 93/560 mg/dl, Gram stain and culture NAD.

Blood culture: No growth.

Course and management: During the second admission she was managed as a case of pneumonia with septicemia with a suspicion of storage disorder. Supplemental oxygen with nasal prong, intravenous fluids, inj ampicillin, gentamycin and cloxacillin were started. Pediatric gastroenterology (PGE) consult was taken and patient was advised to be shifted to PGE after bed availability. At 22 hours of admission, patient started desaturating with pinkish frothy secretions from mouth and altered gastrointestinal (GI) aspirates. Possibility of pulmonary hemorrhage/edema were considered. Endotracheal intubation was done, IPPR started and 10 ml/kg FFP was given. Antibiotics were changed to cefotaxime, amikacin, cloxacillin. Subsequently, she had refractory shock for which inotropic support was started. Preterminally, she had cardiac arrest at 12.55 am on 22/10/11 following which CPR started but patient could not be salvaged. She was declared dead on 22.10.2011 at 1.15 am.

Unit final diagnosis: Pneumonia with septicemia with storage disorder/chronic liver disorder.

Cause of death: Pulmonary hemorrhage/pulmonary edema.

Case Analysis

To sum up this 1-year-old girl, was born of a nonconsanguineous marriage with normal development, presented with fever, progressive pallor and abdominal distension for one and half months, with a superadded history of cough, fever and respiratory difficulty for about a week. On examination, she had hepatosplenomegaly with features of hepatic dysfunction and portal hypertension and superadded pneumonia that precipitated her second admission. She had failure to thrive. Her family history was not significant. Her investigations revealed raised total serum bilirubin and transaminases and severe hepatic synthetic defect. Preliminary investigations revealed a microcytic hypochromic peripheral blood film with normal hemoglobin electrophoresis and bone marrow aspirate.

The approach to this case includes the following:

1. Causes of hepatosplenomegaly with anemia and jaundice in infancy that has rapid progressive hepatic dysfunction and portal hypertension.
2. Causes of acute decompensation and terminal events.

This includes a long list of differentials, but the following pathophysiological categories would be most relevant to this case scenario:

1. *Infection*: Viral hepatitis (A, B, C, D), TORCH (Toxo, CMV, Rubella, Syphilis), Malaria, KalaAzar, Tuberculosis, Fungal, HIV.
2. Hemolytic anemia and myeloproliferative disorders.
3. *Infiltrative-I°*: Hepatoblastoma, Hemangioendothelioma, 2°-leukemia, Lymphoma, Neuroblastoma, Histiocytosis/Hemophagocytic lymphohistiocytosis.
4. Storage/Metabolic
 - Glycogen storage disorders I, III, IV, VI
 - Gauchers-type I, Nieman-Pick type-B
 - Hereditary Tyrosinemia type I
 - Indian childhood cirrhosis.
5. *Chronic liver disorders*: Congenital hepatic fibrosis, autoimmune hepatitis.

Among the infectious causes, since HIV serology was negative and peripheral blood smear did not reveal malarial parasite, it virtually ruled out HIV and malaria. Bone-marrow aspirate did not show any LD bodies and the child had never visited known endemic areas of KalaAzar, ruling out the possibility of KalaAzar. In view of our epidemiology, hepatosplenomegaly and growth failure, tuberculosis could also be considered. However a big sized spleen, transudative ascitic fluid, no history of contact with TB patient and presence of BCG scar, makes this a less likely possibility. The points favoring congenital intrauterine TORCH group of infections was intrauterine growth retardation (birth weight 1500 gm at term), hepatosplenomegaly, anemia, jaundice, failure to thrive, hepatic dysfunction and pneumonia. However, since the patient was asymptomatic till 11 months of age, this possibility was less likely. Also ascitis is not the usual feature in TORCH infections. So, infections as a pathophysiological category looked less likely a cause for this patient.

Hemolytic anemia and myeloproliferative disorders were eliminated as a possible cause since peripheral blood film, hemoglobin electrophoresis and bone-marrow were not suggestive of these disorders.

Among infiltrative disorders, class I histiocytic disorders typically have skeletal system (80%), ear (otitis media, 40%), skin (50%) involvement, which were not present in this patient. Although hepatosplenomegaly and lymphadenopathy favored consideration of histiocytosis, but with a normal bone marrow aspirate it is an unlikely cause to explain the patient's condition. Infection-associated hemophagocytic lymphohistiocytosis (HLH) could also be considered here. The diagnostic criteria described include as follows:

1. Molecular diagnosis consistent with HLH or five of the eight criteria below:
 - Fever
 - Splenomegaly
 - Bicytopenia (Hb <9 gm/dl, plat <100 × 10⁹/l, Neu <1 × 10⁹/l)
 - Hypertriglyceridemia (>3 mmol/l) and/or hypofibrinogenemia (≤1.5 gm/l)
 - Hemophagocytosis in bone marrow, spleen, lymph node or CSF
 - Low/absent NK function
 - Elevated ferritin (>500 µg/l)
 - Soluble CD25 above normal.

Storage disorder	Basic defect	Clinical presentation	Comments
• GSD I (von Gierke)	Glucose-6-phosphatase	Starts in infancy, hepatomegaly, growth retardation, hypoglycemia, acidosis. Mild elevation of transaminases. No Splenomegaly. Renal enlargement also seen. Usually do not develop cirrhosis or hepatic failure.	Less likely
• GSD III (Cori/Forbes/ Limit Dextrinosis)	Debrancher enzyme deficiency IIIa- liver, muscle IIIb- liver	Hepatomegaly, splenomegaly, hypoglycemia, growth failure. Muscle weakness—minimal in childhood. Increases in 3rd/4th decade. No muscular involvement in GSD IIIb Hepatic symptoms improve with age, but in some patients progressive hepatic dysfunction seen.	Possible
• GSD IV (Andersen/ Amylopectinosis)	Branching enzyme deficiency	Classical variety—hepatosplenomegaly, growth failure by 18 months age. Progressive cirrhosis and liver failure (death usually before 5 years)	Possible
• GSD VI (Hers)	Liver phosphorylase	Hepatomegaly, mild hypoglycemia. Progressive course usually not seen	Less likely

Congenital hepatic fibrosis is an autosomal recessive disorder characterized by periportal/perilobular fibrosis with distorted bile duct structures and normal hepatocytes. Cystic dilatation of intrahepatic bile ducts (Caroli disease) and choledochal cyst is also described. The points in favor were hepatosplenomegaly with portal hypertension. But, evidence of hepatocellular dysfunction (raised total bilirubin, transaminitis, hypoalbuminemia, coagulopathy) with normal alkaline phosphatase makes it a less likely possibility.

Storage disorders are a strong contender in this patient in view of massive hepatosplenomegaly, anemia, jaundice and growth failure. While considering storage disorders it would be pertinent to recollect that patient had a normal nervous system examination and developmental milestones. No hypoglycemia or acidosis was documented. So the relevant storage disorders for this patient would include the hepatic, non-neuronopathic types. This includes the following:

1. Glycogen storage disorders (GSD) Type I, III, IV, VI.
2. *Lipid storage disorders*: Lysosomal lipid disorders with predominant hepatic and non-neuronopathic involvement that can be considered in our patient are Gauchers type I and Nieman-Pick type B. Gauchers type I presents with hepatosplenomegaly, thrombocytopenia and skeletal involvement. Pathological hallmark is the Gaucher cell particularly in the bone-marrow. In Nieman-Pick type B, splenomegaly is usually the first manifestation, with or without hepatomegaly. Variable pulmonary involvement with reticular or nodular infiltrates in the lungs. Detection of characteristic Niemann-pick cells in the bone marrow is suggestive of the disease. In view of a normal bone marrow in our patient, these two storage disorders were unlikely.
3. *Hereditary tyrosinemia type I*: These patients have hepatomegaly, jaundice, hypoglycemia and progressive liver failure and cirrhosis. The liver, however, is usually hard and irregular, which was not present in our patient. Additionally, they have renal (metabolic acidosis, rickets, nephromegaly) and peripheral neuropathy (40%) which were lacking in our patient. So this possibility was less likely.
4. *Copper storage disorder*: Indian childhood cirrhosis (ICC)—This disorder is characteristically seen in 6 months to 5 years old. Onset is insidious with distension of abdomen, fever, irritability and altered appetite. Liver is classically firm-hard with sharp 'leafy' edge. Typically, the disease progresses within a few months with hepatosplenomegaly, ascites, edema, jaundice. Palpable gallbladder is due to cholangitis and cholecystitis. Death occurs usually due to bleeding, secondary infection and hepatic coma. Histopathological evidence of orcein-stained copper is the cornerstone of definitive diagnosis. Copper ingestion theory is the most widely accepted theory to explain increased copper in ICC. Boiling or storing milk in untinned brass utensils is often the source, allowing copper to bind to casein in the milk. Genetic susceptibility to copper toxicosis and copper acting in synergy with another hepatotoxin are other plausible pathogenetic theories for ICC. In our patient, the age at presentation, a firm liver with sharp margin on palpation and the rapidity of the progression of hepatic dysfunction, makes Indian childhood cirrhosis a strong possibility.

Factors responsible for decompensation: Several factors described for acute decompensation in patients with hepatic dysfunction are as follows:

- Infection—spontaneous bacterial peritonitis pneumonia
- GIT bleeding
- Electrolyte abnormality
- Medications
- Dehydration
- Large volume paracentesis

In our patient, pneumonia seems to have escalated the acute decompensation.

Preterminal Events

- Pulmonary hemorrhage
- Pulmonary edema
- Refractory shock

Final Diagnosis

- Decompensated liver disease with portal hypertension
- Etiology-Storage disorder: Glycogen storage disorder III or IV or Indian childhood cirrhosis
- Pneumonia (community acquired)
- Pulmonary hemorrhage/edema and refractory shock.

Open House Discussion

- *Prof Vinay Sakhuja*: Thank you Dr Mandeep. The case is now open to the house for discussion. Would anybody from the treating unit like to comment?
- *Senior Resident*: Treating unit—This 1-year-old child presented with anemia, a small head and massive hepatosplenomegaly with some doubtful motor regression. In view of the massive organomegaly, storage disorder was considered as the first possibility. With a massive splenomegaly the first storage disorder thought of is Gauchers or Nieman Pick but the bone marrow did not substantiate the diagnosis which is possible, as in 40% cases. The bone marrow can be negative in the first year and later the storage cells are documented in the liver biopsy or on a serial bone marrow examination. Other storage disorder that can be considered with a massive spleen is glycogen storage disorder type III or IV. Hemophagocytosis can be considered in a child with hepatosplenomegaly but there was no thrombocytopenia.
- *Prof S Singhi*: This patient at 1 year has all features of hepatocellular damage and possibly portal hypertension with failure to thrive and splenomegaly. So the possibility of storage disorder or metabolic disorder leading on to early-onset cirrhosis is the most likely diagnosis. This patient had a cardiac involvement and so the possibility of glycogen storage disorder type IV is high on the cards. Cardiomegaly can be there due to severe anemia. The second possibility is that of Indian Childhood Cirrhosis (ICC) with undiagnosed Gauchers which has not been picked up on bone marrow.
- *Dr Manupdesh*: Glycogen storage disorder does not show cells in the bone marrow as the storage occurs in the hepatocytes. Nieman Pick and Gauchers show the diagnostic cells in the bone marrow in a very high percentage of cases. So the possibility of a storage disorder here seems unlikely.
- *Prof Kartar Singh*: In this case, we have a preserved liver morphology by imaging with an advanced chronic liver disease. The mechanism working here seems to be pericellular fibrosis and so ICC is a strong possibility. The liver has a leafy edge too, which further stands for this diagnosis. Glycogen storage disorder is also a good possibility. Decompensation occurred due to superadded infection.
- *Senior Resident Treating Unit*: In the second admission, we inquired about the usage of copper vessels but the mother negated it. So that is a bit against ICC.

Pathology Discussion—PM 24527: Dr Nandita Kakkar

A complete autopsy was performed on this 1-year-old girl child. The pleural and peritoneal cavities contained 250 and 500 ml of serous fluid respectively. The liver (Fig. 1) weighed 390 gm (Normal for this age—300 gm) was bile stained and the capsular aspect (Fig. 2) showed tiny nodules. The cut section of the liver (Fig. 3) was fibrotic, bile stained with vague nodularity. The portal vein was within normal limits. On microscopic examination, the liver architecture was distorted with fibrous septae forming micronodules (Figs 4 to 6). The fibrous septae show a mononuclear cell infiltrate and prominent bile ductular proliferation (Fig. 6). There was marked hepatocytic damage with abundant Mallory's hyaline present in the cytoplasm of large ballooned hepatocytes (Figs 7 and 8). These are the tangled skeins of intermediate filaments which appear as pink eosinophilic structures within the cytoplasm of the hepatocytes. There was a very extensive pericellular fibrosis (Figs 7 and 8) with fibrosis seen around single to groups of hepatocytes. Cholestasis both hepatocytic and canalicular was seen but no steatosis was present. There was a total absence of regenerative nodules. Orcein stain brought out the abundant presence of cola-colored coarse granules (Fig. 9). Prominent neutrophilic infiltrate was seen to attack the hepatocytes stuffed with Mallory's hyaline. Features are those of a micronodular cirrhosis consistent with



Fig. 1: Gross photograph of the organ complex comprising of slice of the enlarged liver and spleen along with the C loop of the duodenum and the pancreas

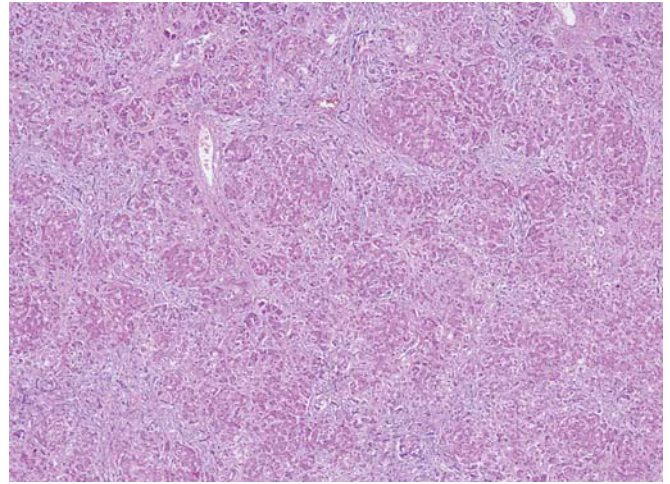


Fig. 4: Microphotograph of the liver at low power showing micronodules cut off by fibrous septae. No steatosis is seen. H and E x 10



Fig. 2: Capsular aspect of the liver showing micronodularity

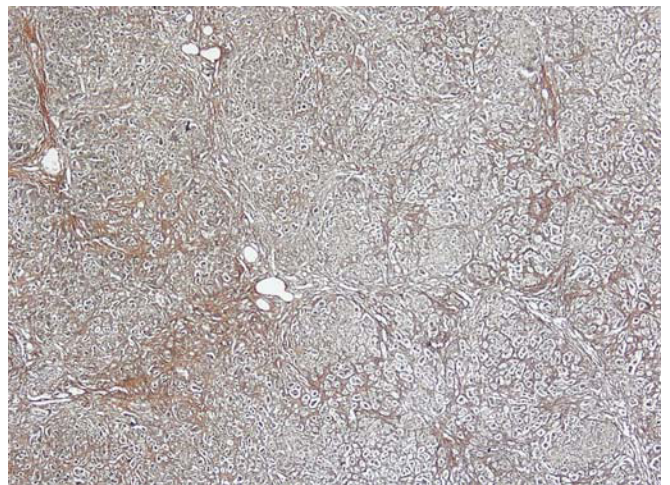


Fig. 5: Reticulin stain showing the presence of fibrous septae forming micronodules. Retic x 10



Fig. 3: Coronal slice of the liver showing bile-stained nodules and interwining fibrosis

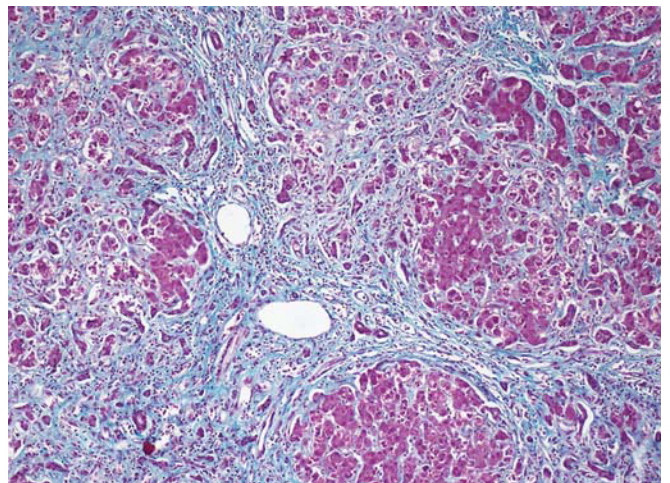


Fig. 6: Masson's trichrome stain showing fibrous septae forming micronodules. The septae show lymphomononuclear cells and bile ductular proliferation. H and E x 20

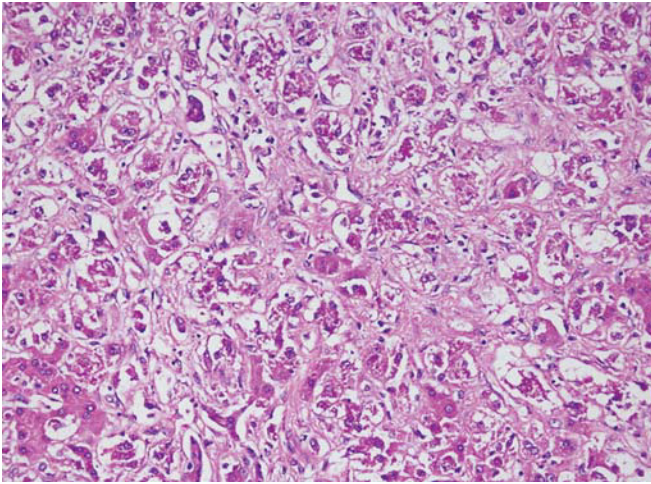


Fig. 7: Microphotograph showing extensive pericellular fibrosis and abundant Mallory's hyaline in the cytoplasm of the large ballooned hepatocytes. H and E x 20

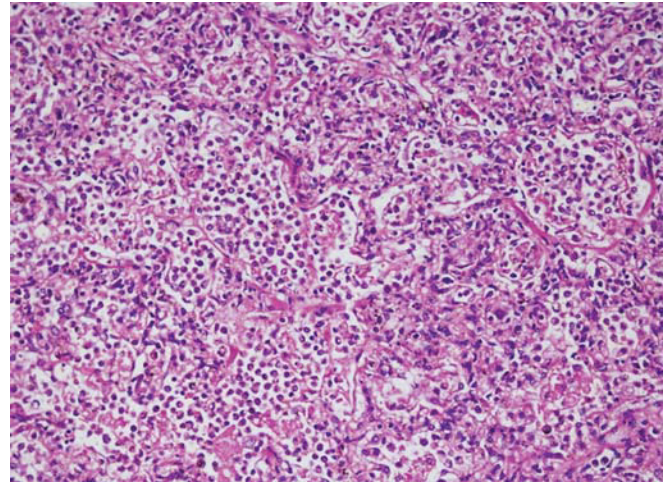


Fig. 10: Microphotograph from the lung showing alveolar spaces packed with polymorphs. H and E x 20

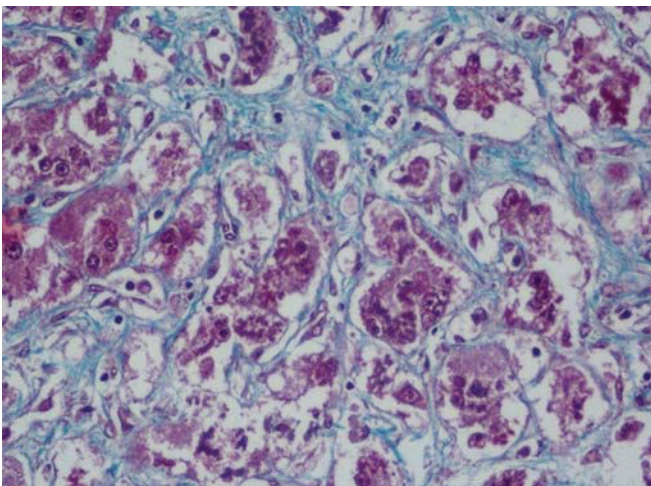


Fig. 8: Masson's trichrome stain showing pericellular fibrosis and Mallory's hyaline. MT x 40

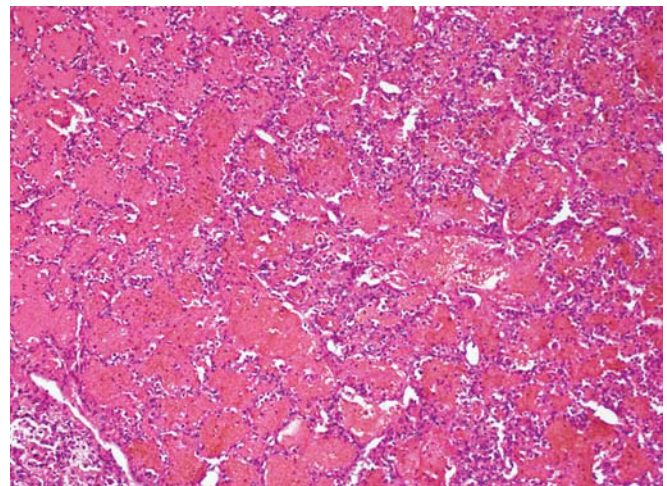


Fig. 11: Microphotograph from the lung showing extensive alveolar hemorrhage. H and E x 20

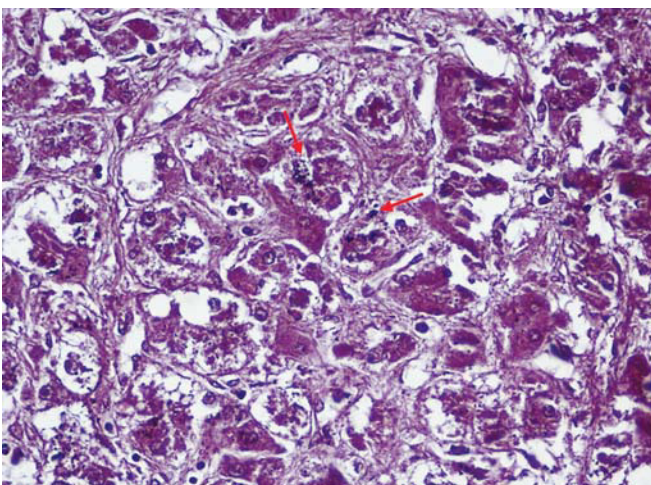


Fig. 9: Orcein stain showing cola-colored coarse granules in the cytoplasm of the hepatocytes (red arrow). Orcein x 20

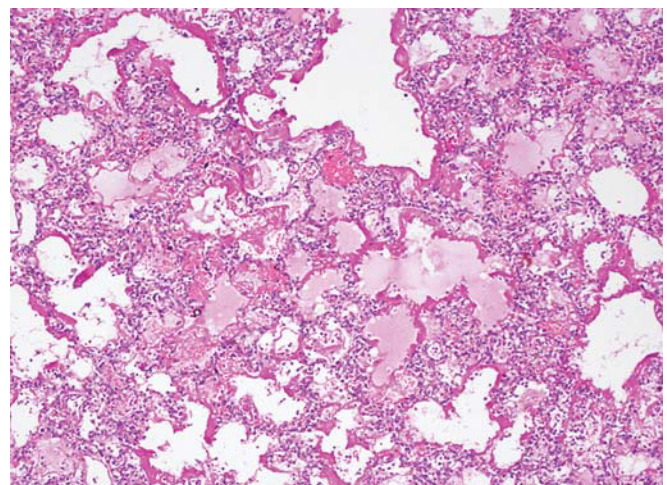


Fig. 12: Microphotograph from the lung showing edema and hyaline membrane formation. H and E x 10

classical Indian childhood cirrhosis. The spleen weighed 100 gm and on microscopic examination revealed marked congestion. Lungs together weighed 140 gm and cut section showed hemorrhagic consolidation. Microscopic examination revealed extensive acute necrotizing pneumonia (Fig. 10). Widespread alveolar hemorrhage (Fig. 11), extensive hyaline membrane formation and edema (Fig. 12) revealed the presence of a widespread diffuse alveolar damage. The bone marrow was normal with adequate representation of all three elements with some histiocytes showing hemophagocytosis. No storage cells were seen. Other organs were within normal limits.

Final Autopsy Diagnosis—PM 24527–1 yr F

- Indian childhood cirrhosis—classical
- Portal hypertension—congestive splenomegaly and ascites
- Acute necrotizing pneumonia with diffuse alveolar damage.

Open House Discussion

- **Prof Vinay Sakhuja:** Thank you Dr Nandita. The entire protocol is now open to the house for discussion.
- **Prof Kartar Singh:** Brass is an alloy of copper and zinc and the proportions of zinc and copper can be varied to create a range of brasses with varying properties. Brass is now being transported to the West. Thanks to the steel revolution that the incidence of ICC has gone down tremendously. Keeping milk or water in brass vessels for long time will lead to contamination. In ICC, ischemic injury occurs due to the pericellular fibrosis.
- **Dr Deepak Bansal:** In how many cases of ICC is the history of copper vessel usage not available? The mother here totally negated the use of copper vessels.
- **Prof S Singhi:** Brass vessels are used for the storage of milk and water. Copper is a bactericidal metal and so the water remains clear as compared to other metals. Many milk vendors supply milk in brass vessels. The description of the liver here is diagnostic of ICC but we got carried away as ICC is rarely seen now. Twenty years back the first diagnosis in this case would have been ICC. The cardiac enlargement in this case seems to be due to anemia.
- **Prof BD Radotra:** ICC disappeared in Maharashtra because the government and the medical fraternity started very strong campaigns against the use of copper vessels. The milk vendors were given incentives and, thus, ICC vanished from Maharashtra. Copper is not the only factor responsible for ICC but there are other theories as well. The paper by Bhavé et al studied the levels of copper after storing the milk and water in copper vessels and found a 60 times increase in copper levels in the milk and a 6 times increase in the water. Many a times the history is not forthcoming. We are getting cases of ICC off and on and so ICC has not completely disappeared.
- **Prof Meenu Singh:** One reason why we went more towards a storage disorder was that the baby had a very large spleen and this normally does not occur in ICC as the hepatocyte damage is very fast, they do not develop portal hypertension but land in a rapid liver failure. Here, the large spleen could be due to an associated hemolysis as the peripheral blood film showed the presence of elliptocytes and target cells. This hemolysis could be due to copper toxicity or due to a concomitant G6PD deficiency.
- **Prof Nandita Kakkar:** We did Prussian blue stains for iron on the sections from the liver, spleen, heart, pancreas and bone marrow but found no increase in the iron stores.
- **Prof S Verma:** I think what Dr Nandita has said has a point. Copper and iron compete with each other for absorption and if you have a copper overload then Fe-deficiency does occur. It would be interesting to study the Fe-status in cases of ICC. There was a microcytic hypochromic anemia and if the child is only on milk then Fe-deficiency occurs as such.

COMMENTARY

Indian Childhood Cirrhosis

ICC is unique to the Indian subcontinent and has fascinated the scientific community for decades. ICC is disappearing from India but scattered reports of ICC-like cirrhosis is appearing in the West. It presents as a chronic liver disease in children between 1 and 3 years of age. Males are affected more than the females and is seen more in families with history of parental consanguinity. ICC affecting siblings is seen in 22%, disease is seen more in rural areas and Hindus are

affected more than the Muslims and Christians. Pathogenesis of ICC is debatable but points toward the dietary copper toxicity. Copper in liver is increased in ICC to more than 800 µg/gm dry weight of liver, the normal being 15 to 55 µg/gm. Other pathogenetic mechanisms are familial, genetic, viral, microbial, toxins and nutritional deficiencies. Copper is known to be cytotoxic and milk boiled in copper vessels, a very common practice in the rural areas leads to a 60 times increase in the copper levels. ICC is now disappearing due to the education being given and due to the use of steel vessels. ICC is treatable with penicillamine and survivors have no apparent evidence of liver disease. In the National Workshop on ICC at Chandigarh in Feb 1987 criteria were laid down for the diagnosis of ICC; (1) Diffuse degeneration of hepatocytes; (2) Absence of distinct regenerative nodules; (3) Presence of abundant Mallory's hyaline; (4) Predominantly neutrophilic infiltrate; (5) Extensive pericellular fibrosis; (6) Diffuse excess of Cu-binding proteins by Orcein stain.

SUGGESTED READING

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