Congenital Hepatic Fibrosis with Polycystic Kidney Disease: An Unusual Cause of Neonatal Cholestasis

VANI BHARANI, *G VYBHAV VENKATESH, #UMA NAHAR SAIKIA AND $BR THAPA

*From Departments of Pathology,*Pediatrics, #Histopathology and $Gastroenterology, PGIMER, Chandigarh, Punjab, India. Correspondence to: Dr Uma Nahar Saikia, Department of Histopathology, 5th floor, Research Block A, Postgraduate Institute of Medical Education and Research, Sector 12, Chandigarh, India. umasaikia@gmail.com*

Received: June 23, 2016; Initial Review: October 13, 2016; Accepted: April 25, 2017.

Congenital hepatic fibrosis is characterized by hepatic fibrosis, portal hypertension, and renal cystic disease. Typical presentation of congenital hepatic fibrosis is in the form of portal hypertension, in adolescents and young adults. We present an unusual case of neonatal cholestasis with rapid deterioration within first 4 months of life, who was diagnosed to have congenital hepatic fibrosis with polycystic kidney disease on autopsy.

Keywords: *Autopsy; Cholestatic Jaundice; Neonate*.

CLINICAL PROTOCOL

History and examination: A 4-month-old child was admitted with complaints of jaundice since day 10 of life, passage of clay colored stool and dark colored urine. He had intermittent high grade fever with dry cough and respiratory distress for 4 days duration. In addition, there was progressive abdominal distension, decreased urine output, irritability, poor feeding and lethargy since 2 days.

Examination revealed pallor, icterus, facial puffiness, and pedal edema. He was febrile with a pulse rate of 128/min. He weighed 4.3 kg, was 59 cm in length and occipitofrontal circumference was 40 cm. There were visible dilated veins over abdomen with presence of free fluid. Liver was palpable 4 cm below right costal margin and was firm, non-tender with smooth surface and irregular borders. Spleen tip was also palpable. Cardiovascular system was unremarkable. The respiratory rate was 58/min, with subcostal retractions and crepitations in bilateral infra-axillary areas. The child was drowsy; however, central nervous system examination was normal. There was no cataract or Kayser–Fleischer ring on ophthalmic examination. The child was developmentally normal and had two elder asymptomatic siblings. He was immunized as per National immunization schedule.

Investigations: He was anemic (Hb 7.9 g/dL), had neutrophilic leukocytosis (WBC count 18,900/µL, 90% polymorphs and 10% lymphocytes) and persistent thrombocytopenia (platelet count 35,000/µL). The coagulogram was deranged (INR 6.8, aPTT >2 min). He had conjugated hyperbilirubinemia (total bilirubin 16.1 g/dL, direct bilirubin 11 g/dL) and transaminitis (AST 774 U/L, ALT 284 U/L). Persistent hyponatremia was recorded (115 meq/L). Random blood sugar was low at 48 mg/dL.

No focus of infection could be identified and peritoneal fluid, urine and blood cultures were sterile. Ultrasonogram (USG) of abdomen showed altered liver echo texture with gross ascites. Gall bladder was mildly distended with edematous wall. No intrahepatic biliary radical dilatation was seen.

Course and management: Lactulose and N acetyl cysteine, intravenous Meropenem and vancomycin were started and Amphotericin B was added later. Hypoglyc3emia was corrected and child was maintained on glucose infusion. An ascitic tap was performed thrice, for symptomatic relief. Albumin could not be administered to correct hypoalbuminemia, due to economic constraints. He received 10 mL/kg of fresh frozen plasma. There was decreased urine output with prerenal azotemia, for which he received slow normal saline bolus. Hyponatremia and hypokalemia were corrected. On day 8 of admission, infant was ventilated due to poor respiratory efforts with falling oxygen saturation. There was a profuse endotracheal tube bleed and the child succumbed to his illness soon after.

Clinical analysis: The infant had cholestatic jaundice, ascites, altered sensorium along with hepatosplenomegaly, deranged liver function tests, deranged coagulogram, anemia and thrombocytopenia. The causes of cholestasis in infancy can be broadly classified as extrahepatic causes like biliary atresia, choledochal cysts and intrahepatic causes including infections, metabolic and genetic conditions. Of the causes of neonatal

cholestasis in north Indian population, biliary atresia is the commonest 34.6 %, followed by idiopathic neonatal hepatitis 24.7 %, sepsis/UTI 19.8 %, metabolic disease like galactosaemia 10.8% and TORCH infections 1.9% [1]. The relevant possibilities are discussed.

The classic features of biliary atresia including jaundice, pale stools and high colored urine along with firm liver [2] were noted in the index case. However, gall bladder was normal on ultrasound. USG has a high overall accuracy in diagnosing biliary atresia [3] whereas clinical signs like persistent clay colored stools have a modest accuracy [4]. A confirmatory Tc99HIDA scan could not be performed to confirm the diagnosis. The infantile variety of choledochal cyst [5] and Caroli's disease [6] can have similar presentations, but were ruled out on imaging.

Infants with metabolic disorders like galactosemia typically present with failure to thrive, vomiting, diarrhea, lethargy, jaundice and cataracts. Edema, ascites, and bleeding can be seen in severe cases. There is an increased risk of overwhelming sepsis, most commonly related to *Escherichia coli* [7]. The present case had acute liver failure with sepsis, encephalopathy and hypoglycemia. However, there was no cataract and urine was negative for reducing substances.

Congenital hepatic fibrosis (CHF) usually presents with signs and symptoms of portal hypertension, although cases presenting in infancy with cholestasis are well known [8]. The rapid deterioration, deranged coagulogram, no intrahepatic biliary tree dilation in the index case is unusual for typical CHF. Synthetic dysfunction of the liver can explain the persistently deranged coagulogram in the index case.

The likely cause of death was overwhelming sepsis, along with acute on chronic liver failure. There was evidence of disseminated intravascular coagulation with pulmonary hemorrhage preterminally.

Open house discussion

Treating unit resident: Clinical scenario is suggestive of a metabolic disease, probably galactosemia. An untreated infant with Classic galactosemia presents as failure to thrive, hepatic injury and sepsis, as seen in the index case. Child was off-milk for few days, which could explain absence of reducing substances in urine. The GALT assay was not preformed due to economic constraints.

Pediatrician 1: In a 4-month-old child, Galactosaemia presenting as cirrhosis with ascites is rather unusual. Biliary atresia has a vast spectrum with varying degrees of obstruction and must be kept as a possibility. Tyrosinemia can also be considered with the clinical picture.

PATHOLOGY PROTOCOL

A complete autopsy was performed with examination of brain. There was peritoneal (200 ml straw colored fluid), pleural (50 ml clear fluid each) and pericardial (40 ml hemorrhagic fluid) effusion.

The liver was enlarged (450 gm) and firm to hard in consistency. The capsular surface showed pin point to pin head sized vague nodules. A fine reticular pattern of fibrosis was seen on cut surface (***Web Fig.* 1a**). Gall bladder, biliary tree, portal and splenic vein were within normal limits. Multiple vague nodules with diffuse periportal fibrosis were seen microscopically (***Web Fig*. 1b, 1c**). There was extensive bile ductular proliferation with circumferential interrupted ring like arrangement, highlighted on CK 7 immunostain, reminiscent of embryonic ductal plate (***Web Fig*. 1d**). Few Von myenberg complexes were also seen. Extensive intrahepatic and intracanalicular cholestasis along with giant cell transformation and pseudoacinar transfor-mation of hepatocytes was noted. Sinusoids showed extramedullary hematopoiesis. There was no evidence of cirrhosis or biliary atresia. No steatosis or significant inflammation was seen. The spleen was enlarged (weight 180 gms) with no significant pathology on microscopy.

The kidneys weighed 110 g with persistent fetal lobulation and numerous pin head sized cysts (***Web Fig*. 2a, 2b**). Numerous cystically dilated tubules arranged perpendicular to the cortex, lined by flattened cells were seen on microscopy (***Web Fig*. 2c**). Glomerulocystic change was seen in <5% glomeruli. Few glomeruli revealed collections of cells with abundant bubbly cytoplasm (***Web Fig*. 2d**), which were positive for CD68 immunostain. Tubules showed bile casts and there was no significant inflammation or fibrosis noted in the interstitium.

The lungs weighed 188 g and showed hemorrhagic consolidation with dull pleura. No thrombi were seen in pulmonary artery and secretions were present in the tracheobronchial tree. Pulmonary hemorrhage was confirmed on microscopy with evidence of hyaline membrane formation. Several bone marrow emboli were noted.

The stomach and esophagus were grossly within normal limits; however, dilated submucosal vessels were seen at gastroesophageal junction on microscopy.

Stress involution changes were seen in the thymus. Lymph nodes revealed sinus histiocytosis. The bone marrow showed adequate representation of all lineages.

The brain weighed 620 g and showed mild cerebral edema. Remaining organs did not reveal any significant pathology.

The final autopsy diagnosis was offered as:

- Congenital hepatic fibrosis, portal hypertension with evidence of splenomegaly, ascites and esophageal varices
- Polycystic kidney disease, possibly Autosomal recessive polycystic kidney disease (ARPKD)
- Bile cast nephropathy
- Diffuse alveolar damage with pulmonary hemorrhages
- Stress involution of thymus

Open house discussion

Pathologist 1: The liver morphology is typical of CHF, though the findings in kidney are more in favor of Autosomal dominant polycystic kidney disease (ADPKD). Short of genetic testing, the parents can be screened to rule out the possibility.

Pathologist 2: The radial cyst arrangement, association with CHF, absence of hepatic cysts and lack of other system involvement are suggestive of ARPKD.

Pediatric gastroenterologist: The index case looks to be the mixed portal hypertensive-cholangitic form of CHF. The usual cholangitic form of CHF has a more protracted course. The cause of persistently elevated INR still remains unclear. Also no source of sepsis could be identified at autopsy.

COMMENTS

CHF is characterized by persistence and/or aberrant remodeling of embryonic ductal plate along with abnormal intrahepatic portal vein branching and progressive portal fibrosis. The age at presentation is highly variable, and most cases are diagnosed in adolescents and young adults. Four clinical forms have been described, portal hypertensive (most common), cholangitic, mixed and latent [9]. Portal hypertension related splenomegaly, hypersplenism and gastrointestinal bleeds are the most common presenting features. Cholestasis and recurrent cholangitis are noted in the cholangitic form, while patients are largely asymptomatic in the latent form with delayed presentation. Liver histology with diffuse periportal fibrosis, irregular islands of hepatic parenchyma and interrupted circumferential arrangement of bile ducts, suggestive of an embryonic ductal plate are diagnostic. Few of the ducts are variably ectatic with intraluminal bile. Collection of acute inflammatory cells can be seen in cholangitic form. The number of portal vein radicals may be reduced. Multiple bile duct hamartomas, von Meyenburg complexes can also be present [10]. In the index case, the morphology of liver was typical of CHF; however the clinical presentation was unusual.

The index case had polycystic kidney disease in association with CHF. The possibilities considered include ARPKD, early-onset ADPKD, Glomerulocystic kidney disease (GCKD), juvenile nephronophthisis and renal dysplasia. ARPKD is characterized by renal enlargement with numerous small cysts in the parenchyma and maintained reniform shape. The cysts originate from collecting ducts, run perpendicular to the cortex and are lined by flattened cells [11]. Most cases are attributed to mutations in the *PKHD1* gene that encodes for fibrocystin/polycystin proteins, involved in maintaining the tubular architecture [12]. *PKHD1* is an exceptionally large gene with over 300 mutations. Four clinicopathological subtypes of ARPKD have been described: perinatal, neonatal, infantile and juvenile, depending on age at presentation and severity of renal and liver disease. In infancy, there is renal enlargement accompanied by oligohydramnios and subsequent pulmonary hypoplasia. In older patients the presenting symptoms are related to liver including hepatosplenomegaly, hypersplenism, variceal bleeding, and cholangitis [13]. A review of 1230 CHF cases showed associated ARPKD in 64% cases [14].

Early-onset ADPKD is a close morphologic differential of ARPKD. Cylindrical cysts lying perpendicular to cortex are typical of ARPKD, and not seen in other cystic renal diseases. The cysts in ADPKD can originate from the entire nephron and are oval in shape. The lining may be cuboidal or flat with intracystic epithelial micropolyps. Glomerulocystic change can be seen in ADPKD and ARPKD, though is more characteristic for ADPKD. The liver shows cysts in cases of ADPKD, while liver fibrosis is common with ARPKD. Glomerulocystic kidney disease (GCKD) is another morphologic differential in the index case. However, glomerulocystic change was seen in <5% glomeruli with renal enlargement, hence GCKD was ruled out. Juvenile nephronophthisis and renal dysplasia were ruled out on morphology [11]. Thus the features were suggestive of ARPKD, based on enlarged kidneys and several cylindrical cysts lying perpendicular to the cortex and associated CHF. Further confirmation by genetic evaluation and parental imaging were not available for the case.

Glomerular foam cells have been demonstrated in hyperlipoproteinemia type III, LCAT deficiency, Lipoprotein glomerulopathy and lysosomal storage

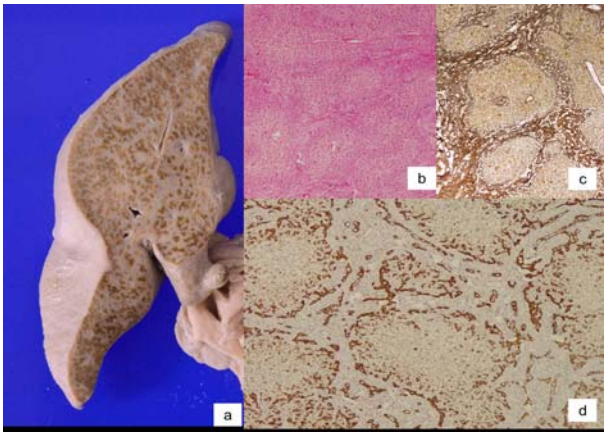
disorders, as well as secondary to focal segmental glomerulosclerosis, diabetic glomerulosclerosis, HIV associated nephropathy and osmotic nephrosis [15]. A lipidogram was done on post mortem serum sample which revealed markedly elevated triglycerides 801mg/dl and low HDL 15 mg/dL. Total cholesterol was 102 mg/dL and LDL was 47 mg/dL. Since the secondary causes can be excluded, these cells could be attributed to dyslipidemia.

This was a case of cholestasis of infancy with deterioration within first 4 months of life found to have CHF with polycystic kidney disease on autopsy. Presentation in infancy with cholestasis and features of portal hypertension were the unusual features in this case. The associated cystic kidney disease was identified only at autopsy, which could have been identified antemortem if a complete rather than a limited abdominal imaging were performed. Also findings of glomerular foam cells, associated with dyslipidemia have not been seen in the above clinical setting before.

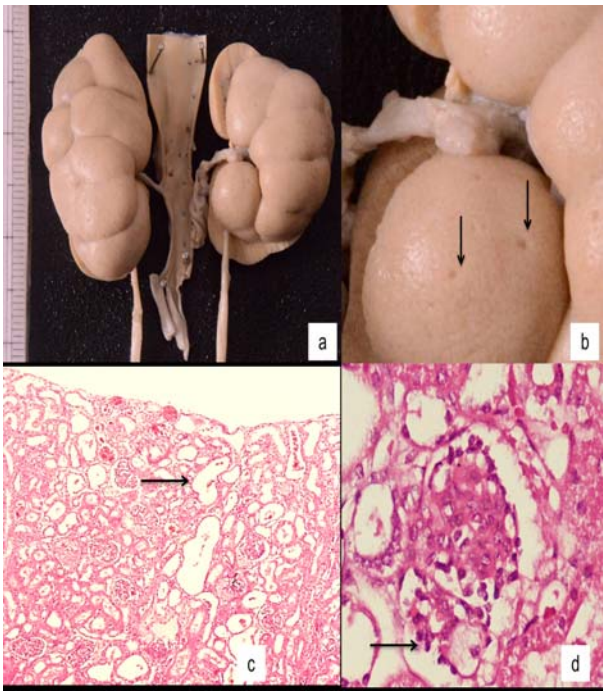
Contributors: VB, UN: Pathological evaluation at autopsy, preparation of manuscript, VV and BRT: Clinical management of the patient and clinical discussion.
Funding: None; *Competing interest*: None stated.

REFERENCES

1. Poddar U, Thapa BR, Das A, Bhattacharya A, Rao KL, Singh K. Neonatal cholestasis: differentiation of biliary atresia from neonatal hepatitis in a developing country. Acta Paediatr. 2009;98:1260-4.
2. Ramachandran P, Safwan M, Reddy MS, Rela M. Recent trends in the diagnosis and management of biliary atresia in developing countries. Indian Pediatr. 2015 ;52:871-9.
3. Humphrey TM, Stringer MD. Biliary atresia: US diagnosis. Radiology. 2007~244:84551.
4. Hsiao CH, Chang MH, Chen HL, Lee HC, Wu TC, Lin CC, *et al*. Universal screening for biliary atresia using an infant stool color card in Taiwan. Hepatology. 2008~47:1233-40.
5. Mishra A, Pant N, Chadha R, Choudhury SR. Choledochal cysts in infancy and childhood. Indian J Pediatr. 2007;74:937-43.
6. Ananthakrishnan AN, Saeian K. Caroli's disease: identification and treatment strategy. Curr Gastroenterol Rep. 2007;9:151-5.
7. Berry GT. Classic galactosemia and clinical variant galactosemia. *In*: Pagon RA, Adam MP, Ardinger HH, Wallace SE, Amemiya A, Bean LJH, *et al*., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2016. Available from: *http://www.ncbi.nlm.nih.gov/books/NBK1518/*. Accessed April 13, 2016.
8. Nazer H, Nazer D. Congenital hepatic fibrosis. Medscape. Updated: Mar 31, 2014. Available from: *http://emedicine.medscape.com/article/927984-overview*. Accessed April 13, 2016.
9. Fauvert R, Benhamou JP. Congenital hepatic fibrosis. *In:* Schaffner F, Sherlock S, Leevy CM, editors. The Liver and its Diseases. New York: Intercontinental Medical Book; 1974. p. 283-8.
10. Gunay-Aygun M, Gahl WA, Heller T. Congenital Hepatic Fibrosis Overview. 2008 Dec 9 [updated 2014 Apr 24]. *In*: Pagon RA, Adam MP, Ardinger HH, Wallace SE, Amemiya A, Bean LJH, *et al.;* editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2016. Available from: *http://www.ncbi.nlm.nih.gov/books/NBK2701/PubMed.* Accessed April 13, 2016.
11. Liapis H, Winyard P. Cystic diseases and developmental kidney defects. *In*: Jennette JC, Olson JL, Schwartz MM, Silva FG, eds. Hepinstall's Pathology of the Kidney. Philadelphia: Lippincott Williams & Wilkins; 2007. p. 1258-1307.
12. Gunay-Aygun M, Avner ED, Bacallao RL, Choyke PL, Flynn JT, Germino GG, *et al*. Autosomal recessive polycystic kidney disease and congenital hepatic fibrosis: summary statement of a first National Institutes of Health/ Office of Rare Diseases conference. J Pediatr. 2006;149:159-64.
13. Ward CJ, Hogan MC, Rossetti S, Walker D, Sneddon T, Wang X, *et al*. The gene mutated in autosomal recessive polycystic kidney disease encodes a large, receptor-like protein. Nat Genet. 2002;30:259-69.
14. Srinath A, Shneider BL. Congenital hepatic fibrosis and autosomal recessive polycystic kidney disease. J Pediatr Gastroenterol Nutr. 2012~54:580-7.
15. Porubsky S, Kuppe C, Maier T, Birk HW, Wörnle M, Moeller MJ, *et al*. Renal lipidosis in patients enrolled in a methadone substitution program. Arch Pathol Lab Med. 2014;138:689-93.



WEB FIG. 1 *Liver: (a): Cut surface with fine reticular fibrosis; (b and c): Multiple vague nodules with diffuse periportal fibrosis (H&E, reticulin x 10X); (d): CK 7 highlighting the interrupted ring arrangement of bile ducts (IHCx10X).*



WEB FIG. 2 *Kidneys: (a): Enlarged with persistent fetal lobulation; (b): Numerous pin head size cysts; (c): Cysts arranged perpendicular to cortex (H&Ex 10X); (d): Glomerular foam cell (H&Ex 40X).*