

USCAP
PEDIATRIC PATHOLOGY
Slide Session

CASE 4

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Patient 1 – Slide B

- Twin A: 27 4/7 wk gestation; 1090 gm
- Maternal gestational DM, ITP - Rx IVIG
- Ventilatory support for 3 months
- Multiple episodes of sepsis
- TPN from Day 2 to 16, w trophic feeds; enteral intake adequate thereafter

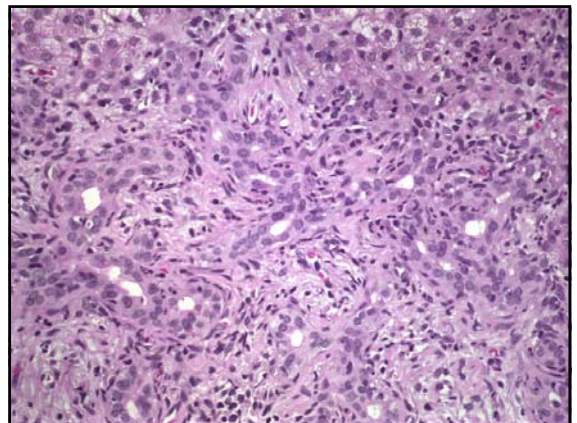
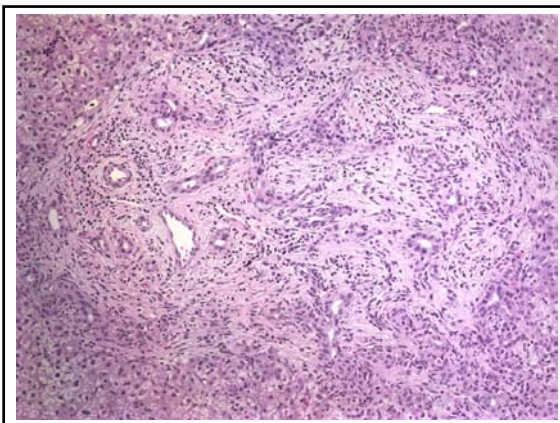
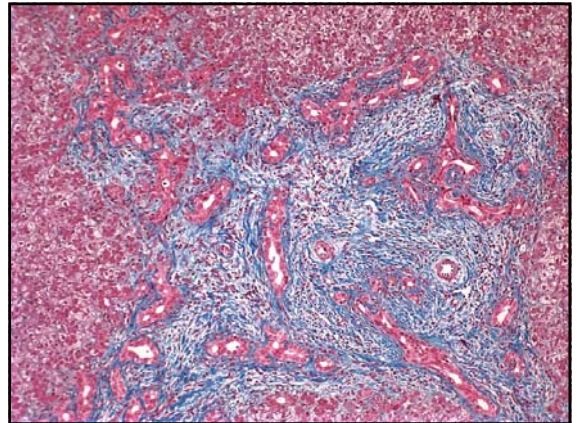
•Bc 2.8 day 5, 1.7 at one month, 3.8 at 3 mo, with AST 84, ALT 59, AlkP 47, GGT 556

•Serial abd **Ultrasound**: hyperechoic liver, contracted GB; no duct dilatation in liver

•**HIDA** at 3mo: poor uptake, no excretion

•**Stool** color not mentioned in chart until now

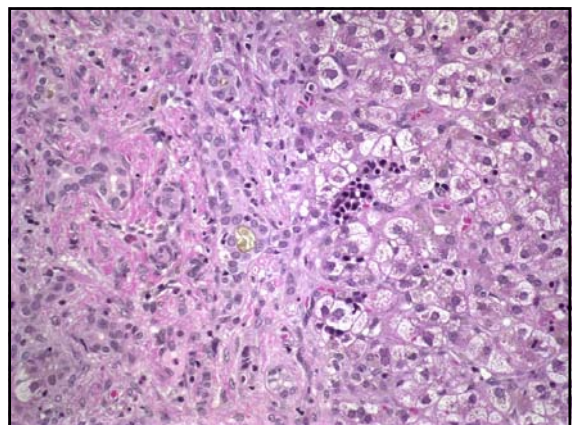
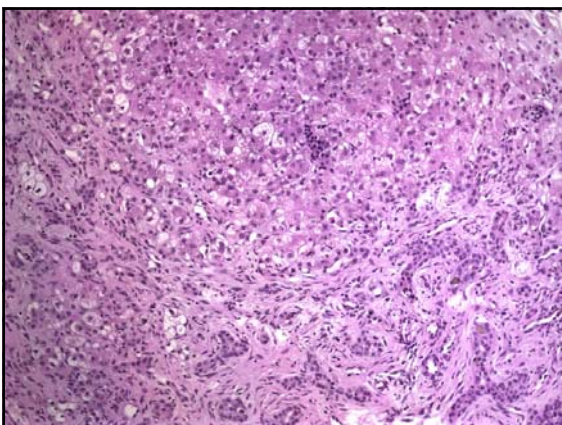
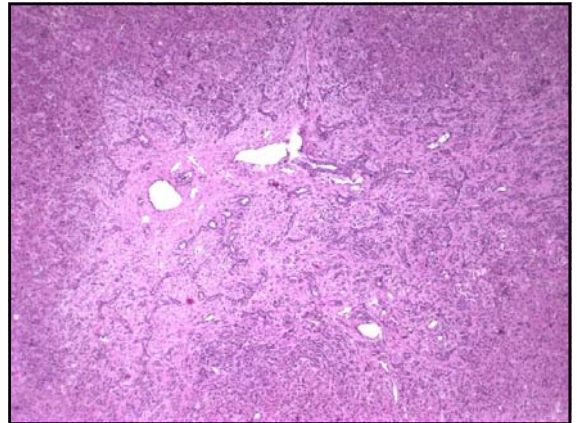
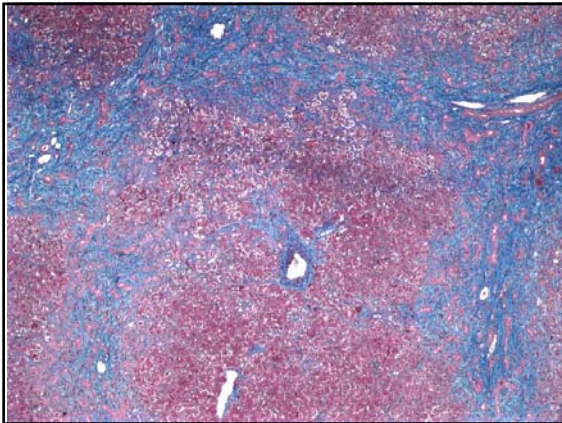
•**Liver biopsy**: DOL 145

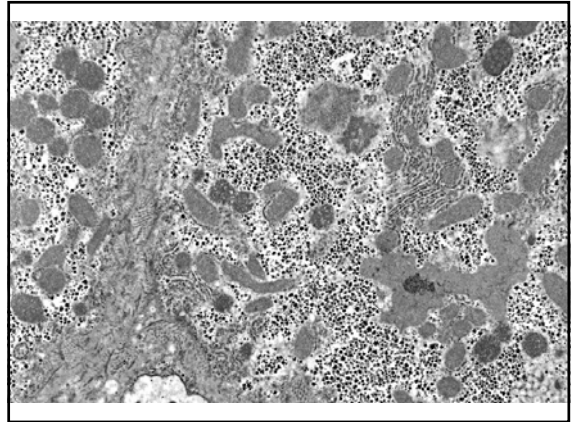
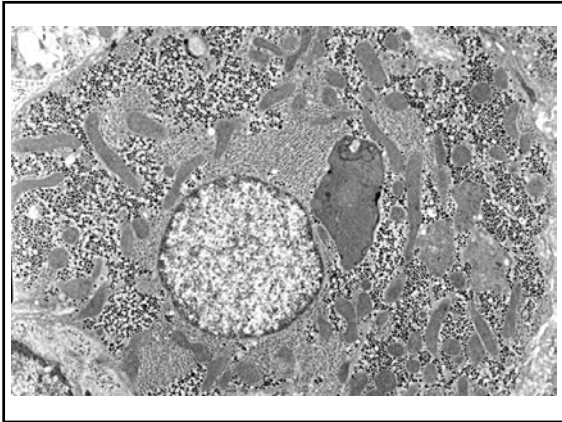


Patient 2 – Slide A

- Twin B – 31 3/7 gestation, 828 gm
- Hypoglycemia – no lactic acidosis but urinary organic acids suggested abnormal gluconeogenesis
- RDS >>> BPD; peripheral pulmonic stenosis
- Microcephaly – no CNS symptoms or signs
- Metaphyseal dysplasia
- Multiple infections
- Abd Ultrasound: ascites, contracted thick GB; no organ abnormalities

- TPN exclusively until Day 21; then feeding began
- On transfer at 90 days, anemia, thrombocytopenia; PT and PTT prolonged
- **Bc 1.5, AST 82, ALT 101, AlkP 829, GGT 66**
- **HIDA:** poor uptake but with excretion
- **Liver biopsy – day 105**





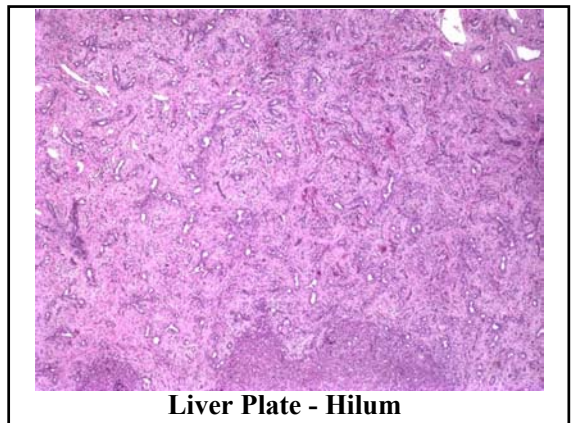
Biopsy Diagnosis of Biliary Atresia

- Bile duct proliferation with bile plugs and acute cholangitis
- Ductular proliferation at interface of expanded tracts, with bile plugs, PMN;s
- Portal edema and fibrosis, with mixed WBC infiltrate
- *Variable parenchymal cholestasis, giant cells, EMH --- non-specific*
- (Russo P, Ruchelli E, Piccoli DA. **Pathology of Pediatric Gastrointestinal and Liver Disease**, Springer-Verlag, New York, 2004, page 203)

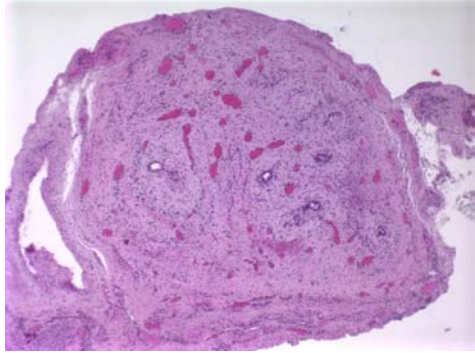
Alternative Diagnoses in a First Biopsy

1. If early, maybe no duct proliferation
2. Obstruction from choledochal cyst, perforated duct, myofibroblastic tumor, other mass lesion
3. Obstruction due to "sludge" in association with parenteral nutrition, lack of oral intake
4. Cystic fibrosis
5. Alagille syndrome
6. Congenital Cytomegalovirus infection
7. Alpha 1-Antitrypsin deficiency
8. North American Indian cirrhosis (*CIRH1A* mutation)
9. PFIC 3 (high GGT) – *MDR 3, ABCB4*.

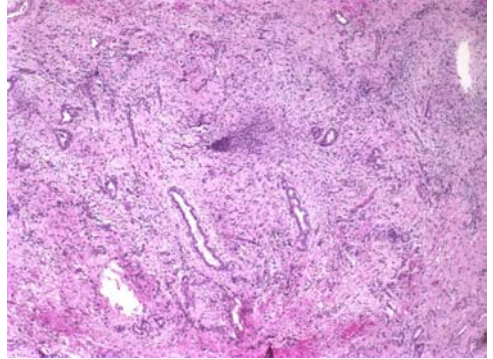
Patient 1
after biopsy



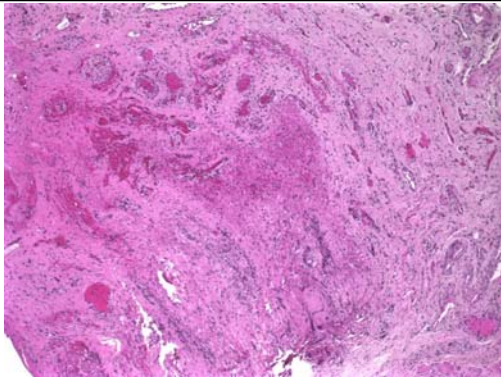
Liver Plate - Hilum



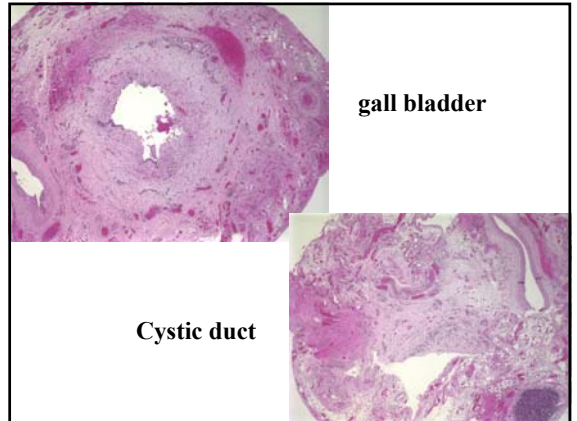
“collateral veins” = proximal Hepatic duct



Common hepatic duct remnant



Common bile duct – distal end



gall bladder

Cystic duct

Subsequent Course

- Patient 1 - post-Kasai
- Bc fell steadily from 6.5 to 1.0 on day 16 and remains Zero at 3 mo.
- However, GGT has climbed from 457 to 1197 in the same interval
- Infant had multiple infections – meningitis, possible cholangitis

Questions Raised

- 1. Differential diagnosis of conjugated bilirubinemia in **prematures**
- 2. Pathogenesis of **Acquired** Atresia
- 3. Prognosis for Patient 1
- 4. How long after TPN is stopped does jaundice persist, and why?
- 5. What is disease in patient 2?

Pathogenesis of Biliary Atresia

- 1. Is there a fetal-embryonal form and does it correspond to the minority “Syndromic” disease? (Developmental malformation theory)
- 2. Is there a molecular genetic basis?
- 3. Is it Inflammatory, or Immunologic, maybe with an Infectious origin?
- 4. Could it be Vascular?

References

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- Michel E et al **Biliary atresia due to delayed maturation of the gut hormones system?-introducing a new treatment modality.** *J Perinat Med* 2004; 32: 288
- Davenport M. **A challenge on the use of the words Embryonic and Perinatal in the context of biliary atresia.** *Hepatal* 2005; 41:403 (with response from Bezerra and Sokol, 404)
- Gaudio E et al. **Administration of r-VEGF-A prevents hepatic artery ligation induced bile duct damage in bile duct ligated rats.** *Am J Physiol Gastrointest Liver Physiol* 2006; 291: G307
- Xia X et al. **Bile acid interactions with cholangiocytes.** *World J Gastroent* 2006;12: 3553.
- Mack CL et al. **Cellular and humoral autoimmunity directed at bile duct epithelia in murine biliary atresia.** *Hepatal* 2006; 44:1231.

Prognosis

- 1. Is earlier porto-enterostomy beneficial?
- 2. Is PE after 60 days doomed to fail?
- 3. Does bile flow post- Kasai or Bc predict long-term outcome?
- 4. What other features influence rate of progression?
- 5. Are there interventions available short of transplantation?

References

- Volpert D, White F, et al **Outcome of early hepatic portoenterostomy for biliary atresia.** *JPGN* 2001; 32: 265
- Shneider BL et al (BARC). **A multicenter study of the outcome of Biliary Atresia in the United States, 1997-2000.** *J Pediatr* 2006; 148: 467
- Chardot C, Serinet M-O. **Prognosis of Biliary Atresia: what can be further improved?** *J Pediatr* 2006; 148: 432

“TPN”- related biliary disease

- 1. Severity and rate of progression worst with extreme prematurity
- 2. All portal tract features can be seen by 10 days (duct proliferation, bile plugs, PMN)
- 3. Hilar ducts may be inflamed by two weeks
- 4. Biliary cirrhosis (portal bridging) may be present by one month
- 5. Bc elevations may persist for weeks after oral intake begins
- 6. In term infants with Short gut, intestinal transplant can reverse hepatic dysfunction, maybe even degree of scarring

References

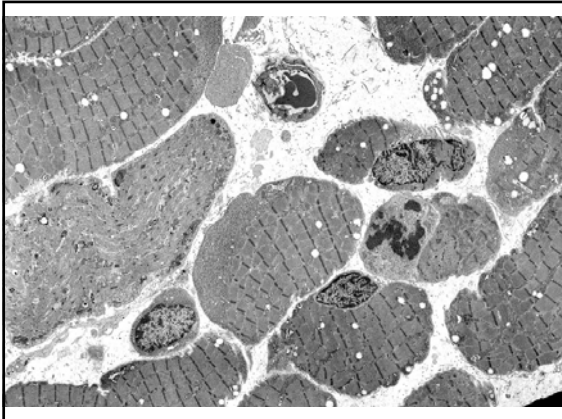
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- Rager R, Finegold, MJ. **Cholestasis in premature infants: Is parenteral alimentation responsible?** *J Pediatr* 1975; 86: 264
- Chen CY et al. **UCDA therapy in very-low birth weight infants with TPN-associated cholestasis.** *J Pediatr* 2004; 145: 317
- Iyer KR et al. **Functional liver recovery parallels autologous gut salvage in short bowel.** *J Pediatr Surgery*; 2004; 39: 340
- Javid PJ et al. **The role of enteral nutrition in the reversal of TPN-associated liver dysfunction in infants.** *J Pediatr Surg* 2005; 40:1015

Further Diagnostic study of Patient 2

- Normal **karyotype**
- Normal plasma **amino acids**
- No urinary succinyl acetone
- Normal **NMR spectroscopy** of basal ganglia
- Normal Transferrin **isoelectric focusing**,
- **Niemann-Pick A, B, C** excluded.

Muscle Biopsy – 4 months

- **Morphology**: marked fiber size and shape variation; excess glycogen and lipid; Z band streaming
- **ETC activity reduced** in all complexes but not to diagnostic levels
- **No Mutation** in *POLG1*, *DGK*, *MPV17*, *TK2* (1st 3 are associated w *mtDNA depletion syndrome and Hepatic failure*)



Outcome for Patient 2

- **Died** 2 months after biopsy with ischemic necrosis of small bowel
- **Biliary Cirrhosis**
- **Neuronal migration disorder** with cerebral heterotopias, microdysgenesis
- **Etiology undeterminedbut, identical (monozygotic) twin is unaffected!**

References –patient 2

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- Ferrari, G.; **Infantile hepatocerebral syndromes associated with mutations in the mitochondrial DNA polymerase-gamma A.** *Brain* 128: 723-731, 2005
- Mancuso, M.; **New DGK gene mutations in the hepatocerebral form of mitochondrial DNA depletion syndrome.** *Arch. Neurol.* 62: 745-747, 2005
- Spinazzola, A.; **MPV17 encodes an inner mitochondrial membrane protein and is mutated in infantile hepatic mitochondrial DNA depletion.** *Nature Genet.* 38: 570-575, 2006.