

Slides Seminar

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Diagnosis. Biliary cirrhosis due to chronic cholangiopathy in an adult caused by multidrug-resistance 3 (MDR3) gene *ABCB4*

Pathological findings

Section of a representative tissue block from a hepatectomy specimen removed at transplantation.

An advanced biliary type cirrhotic liver with broad portal based and bridging fibrous septa delineating irregularly shaped, but predominantly small parenchymal nodules. Of note is the biliary interface activity including the formation of a pale halo characteristic of long-standing cholangiopathy, subtle ductular reaction, Mallory bodies, cholestasis and fair amount of orcein-positive copper-associated granules. The genuine bile ducts appear focally reduced in number as evidence by arterial branches unaccompanied by bile duct of matching size. The section includes a large bile duct with inspissated bile in the lumen which is made of cholesterol and bilirubin.

Differential diagnosis

Primary biliary cirrhosis (PBC) and sclerosing cholangitis (PSC) are main differential diagnoses histologically.

Granulomatous bile duct destructions, not seen here, may be absent in late stage of the disease and characteristic fibro-obliterative lesions may similarly be missing in PSC.

Clinically the patient is AMA negative and young for a PBC, stage 4.

A young brother and a sister similarly affected would be exceptional with PBC, practically unknown in PSC and suggest adult presentation of a metabolic / metabolic disorder.

Genomic study revealed 2 different parental mutations in the *ABCB4* locus encoding MDR3 protein (chromosome 7), both mutations detected in the 3 affected children. In infants with MDR3 deficiency the complete loss of MDR3 protein can be demonstrated by immunohistochemistry, unfortunately not in adults. Some cases of 'idiopathic' biliary cirrhosis in young adults and adulthood ductopenia may be example of unrecognized MDR3 deficiency.

Class III multidrug resistance P-glycoproteins, *mdr2* in mice and MDR3 in humans, are canalicular phospholipid translocators involved in biliary phospholipid excretion. MDR3 deficiency leads to an absence of phospholipids, deficient bile acids mixed micelles formation and extremely hydrophobic bile which is damaging to bile duct epithelium.

References

Portmann BC, R Thompson, E. Roberts, A. Paterson. (2007) Genetic and metabolic liver disease. In A D Burt, B C Portmann, L Ferrell (eds) *MacSween Pathology of the Liver*, 5th edn. Edinburgh: Churchill Livingstone – Elsevier pp 199-326

de Vree JM, Jacquemin E, Sturm E et al. Mutations in the MDR3 gene cause progressive familial intrahepatic cholestasis. *Proc Natl Acad Sci USA*, 1998; 95:282–287

Elferink RP, Tytgat GN, Groen AK. Hepatic canalicular membrane 1: The role of *mdr2* P-glycoprotein in hepatobiliary lipid transport. *Faseb J*, 1997; 11:19–28

Lucena JF, Herrero JJ, Quiroga J et al. A multidrug resistance 3 gene mutation causing cholelithiasis, cholestasis of pregnancy, and adulthood biliary cirrhosis. *Gastroenterology*, 2003; 124:1037–1042

Sundaram SS, Sokol RJ. The multiple facets of *ABCB4* (MDR3) deficiency. *Curr Treat Options Gastroenterol*. 2007;10:495-503

Gotthardt D, Runz H, Keitel V, et al. A mutation in the canalicular phospholipid transporter gene, *ABCB4*, is associated with cholestasis, ductopenia, and cirrhosis in adults. *Hepatology*. 2008;48:1157-66