Diagnostic Exercise
From The Davis-Thompson Foundation*

Case #: 77 Month: February Year: 2017

Answer Sheet

Contributor: Catherine A. Picut, VMD, JD, DACVP, DABT, FIATP, Senior Staff Pathologist, Charles River-Pathology Associates, Durham, N.C.

Clinical History: This Sprague Dawley Rat (Cr1:CD(SD)) was 17 weeks old at the end of a 28-day study. This particular rat was from the adjuvant-control group and did not receive the test article. There were no clinical signs and the animal survived until scheduled sacrifice.

Morphologic diagnosis: Cystic tubular dilatation with fibrosis, severe, disseminated, kidney

Other organ likely affected: Liver (see additional microscopic images below, Figures 5-6)

Figure 5. Liver, H&E, 1.85x (left) and 10x (right) objective magnification. Note multiple saccular distention of bile ducts and the portal and bridging fibrosis associated with dilated bile ductules and ducts.
Figure 6. Liver, H&E, 40x objective magnification. Note periportal fibrosis with multiple dilated bile ducts, each lined by plump cuboidal epithelium.

**Cause:** Genetic mutation

**Etiologic diagnosis:** Congenital polycystic kidney disease and Congenital intrahepatic biliary dilatation with fibrosis

**Name of this condition:** Caroli’s Disease

**Typical gross findings:** Enlargement and multiple cysts in the kidney and liver

**Typical microscopic findings:** Cystic distention of renal tubules and bile ducts with associated peritubular and periductular fibrosis, respectively.

**Discussion:** Congenital polycystic kidney disease with intrahepatic biliary dilatation and fibrosis is an autosomal recessive condition in man known as Caroli’s disease or Caroli’s syndrome. This multi-organ developmental disease has been described in the rat (Sanzen et al. 2001; Katsuyama et al. 2000; Bettino et al. 2003), mouse (Moser et al. 2005), dog (Gorlinger et al. 2003) and goat (Hananch and Faizee 2014). The malformation in the liver is due to impaired remodeling of the fetal ductal plate (the precursor of the intrahepatic biliary system) and is commonly associated with portal fibrosis. The underlying lesion in the liver is a ductal plate malformation, and bile ducts are more numerous than usual. A similar deranged epithelial-mesenchymal tissue induction occurs in the kidney leading to malformation and cystic distention of renal tubules. The pathogenesis of this multi-organ syndrome is likely related to fibrocystin, which is a large protein encoded by the *polycystic kidney and hepatic disease 1 (PKHD1)* gene (Menezes and Onuchic, 2006).
In rats, enlargement and cysts of the liver and kidney are grossly observed at 3 weeks of age with increase in severity and progression of the lesion (i.e., larger cysts and fibrosis) up to 4 months of age. The renal cysts begin at the corticomedullary junction and expand into the cortex, generally sparing the renal papillae and glomeruli. The cysts in the liver are confined to the liver, but distention of the extrahepatic bile duct is possible. Elevation of serum chemistry parameters is variable. In this particular case presentation, the liver and kidney weights of the affected rat were higher than those weights of other control rats, and mild elevation of BUN was the only clinical pathology finding. Inflammation may co-exist in the periportal regions and in the affected kidneys, but the inflammation is secondary. Occasional intratubular granular casts were present in the kidney of this case.

In human cases of Caroli’s syndrome, dilated bile ducts are prone to development of cholangitis/cholangiohepatitis, intraductal lithiasis, cirrhosis, portal hypertension, and cholangiocarcinoma, and the polycystic kidneys may be accompanied by chronic renal disease and rickets (Shenoy 2014).

Caroli’s disease or syndrome (involving liver and kidney) should be differentiated from cystic congenital malformations limited to the liver, the latter being reported in the cat (Zandvliet et al. 2005), calf (Yoshikawa et al. 2002), foal (Haechler et al 2000) and non-human primate (Wallace et al. 2009).

References:


*The Diagnostic Exercises are an initiative of the Latin Comparative Pathology Group (LCPG), the Latin American subdivision of The Davis-Thompson Foundation. These exercises are contributed by members and non-members from any country of residence. Consider submitting an exercise! A final document containing this material with answers and a brief discussion will be posted on the CL Davis website (http://www.cldavis.org/diagnostic_exercises.html).

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