Experimental and Toxicologic Pathology 67 (2015) 361–364

Contents lists available at ScienceDirect

Experimental and Toxicologic Pathology

journal homepage: www.elsevier.de/etp

Short Communication

Polycystic kidney disease in Sprague-Dawley rats

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ARTICLE INFO

Article history:
Received 8 October 2014
Accepted 12 February 2015

Keywords:
Sprague-Dawley rat
Polycystic kidney disease
Kidney
Liver
Histopathology

ABSTRACT

Polycystic kidney disease (PKD) is a cystic genetic disorder of the kidneys which is typically associated with cystic bile duct dilatation in the liver in humans, and domestic and laboratory animals. In humans, there are two types of PKD, autosomal dominant polycystic kidney disease (ADPKD) and autosomal recessive polycystic kidney disease (ARPKD). ADPKD is caused by mutations in *PKD1* or *PKD2* gene while ARPKD is caused by mutation or loss of the *PKHD1 (polycystic kidney and hepatic disease 1)* gene. Here we report a morphologically confirmed case of spontaneous PKD in a Sprague-Dawley rat in which anatomic pathology examination revealed numerous cystic changes in the kidney and liver. Lesions consisted of marked cystic dilatations of renal tubules, and moderate cystic dilatations of intrahepatic bile ducts with portal fibrosis. We present detailed histologic features of the spontaneous PKD and compare them with disease model rats carrying an autosomal recessive *PKHD 1* gene mutation.

1. Introduction

Polycystic kidney disease (PKD) is a cystic genetic disorder of the kidneys which has been associated with cystic bile ducts, bile duct proliferation, and/or cystic pancreatic ducts. In humans, there are two types of PKD: autosomal dominant polycystic kidney disease (ADPKD) and autosomal recessive polycystic kidney disease (ARPKD). ADPKD is caused by mutations in one of two genes, *PKD1* or *PKD2*, while ARPKD is caused by mutation or loss of the *PKHD1* gene (Ward et al., 2002; Torres et al., 2007). In the more common form, ADPKD, the renal parenchyma is extensively replaced by cysts that originate from all segments of the nephron, collecting tubules, and ducts. In humans with ADPKD, there is an association with cysts in other organs, most often the liver. Other abnormalities that can be coupled with ADPKD include cardiac valvular anomalies, intracranial aneurysms, and colonic diverticula. In ARPKD, cysts arise from only dilated collecting tubules and ducts and in most cases there is also intrahepatic biliary cysts and hepatic fibrosis (Flaherty et al., 1995; Martinez and Grantham, 1995). In animals, familial/hereditary PKD has been recognized in many species including dogs, goat, mouse, and rats (Katsuyama et al., 2000; Krotec et al., 1996; O'Leary et al., 1999; Takahashi et al., 1986). The potential utility of an animal model of human diseases depends on how well it mimics the disease as well as genetic uniformity, reproduction rate, cost, etc. A rat model of ARPKD derived from Sprague-Dawley strain has shown PKD with an autosomal-recessive inheritance pattern and hepatic involvement in the disease, which resembles human condition (Katsuyama et al., 2000; Kai et al., 2001; Sanzen et al., 2001). The rat ARPKD model originally stems from a spontaneous mutation in a strain of Sprague-Dawley rat (Katsuyama et al., 2000).

This report characterizes the morphologic features of a spontaneous PKD in a Sprague-Dawley rat and compares its morphology with Sprague-Dawley rat model of ARPKD carrying an autosomal recessive *PKHD1* gene mutation.

2. Materials and methods

2.1. Animals

The animal with spontaneous PKD was a 14 weeks old, male, Sprague-Dawley rat (Crl:CD®[SD]) allocated to a control group administered a vehicle (0.02% polysorbate 80, 0.66 mL/kg) via the tail vein once every other week for a 7-week non-clinical toxicity study. During the study, clinical signs were observed daily. Standard hematology (red blood cell mass parameters, reticulocytes, white blood cells, white cell differential, and platelets) and serum chemistry (blood urea nitrogen, creatinine, sodium, chloride, phosphorus, potassium, calcium, total protein, albumin, globulin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, gamma-glutamyl transferase, total bilirubin, glucose, and cholesterol) examinations were conducted. For

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http://dx.doi.org/10.1016/j.etp.2015.02.002
0940-2993/

Table 1
Incidence and severity of cystic changes in the kidney and liver.

		ARPKD model		Spontaneous PKD	
Organ Finding		Kidney Cystic tubules	Liver Cystic bile ducts	Kidney Cystic tubules	Liver Cystic bile ducts
Severity	+	1 (3.3%)	–	–	–
	++	14 (46.7%)	24 (80%)	–	–
	+++	15 (50.0%)	6 (20%)	–	1
	++++	–	–	1	–
Total		30	30	1	1
No. examined		30	30	1	1

comparison of morphologic tissue abnormalities, 30 male ARPKD model rats homozygous for mutation at the *PKHD1 locus* (PCK/CrljCrl-Pkhd1pck/CRL) were used. The ARPKD model rats ranged in age from 23 to 26 weeks old. All procedures performed on animals were in accordance with regulations and established guidelines, and were reviewed and approved by the Pfizer Institutional Animal Care and Use Committee.

2.2. Tissue preparation

Tissue samples from kidney and liver were collected in 10% neutral buffered formalin. Tissues were trimmed, embedded in paraffin, sectioned at approximately 5 μm, and stained with hematoxylin and eosin (H&E).

2.3. Grading system for lesions in the kidney and liver

Cystic lesions in the kidney and liver were graded by microscopic examination to obtain a comprehensive assessment of the severity based on the following semi-quantitative grading scheme, which was modified from Kai and others (Kai et al., 2001).

Kidney

- Marked (++++) = Presence of numerous large cystic (dilated) tubules, which occupy greater than 75% area of the outer medulla and widely extend over the cortex.
- Moderate (+++) = Presence of several large cystic (dilated) tubules, which occupy 51–75% area of the outer medulla and often extend to the inner cortex.
- Mild (++) = Same as moderate, but 26–50% of the outer medulla was occupied by the cystic tubules.
- Minimal (+) = Presence of a few smaller cystic tubules occupying up to 25% area of the outer medulla.

Liver

- Moderate (+++) = Presence of cystic structures which were divided into variable-sized compartments, and several cystic structures were dilated up to the size of several liver lobules.
- Mild (++) = Presence of variable-sized cystic structures which were up to the size of one liver lobule.

3. Results

A summary of microscopic observations is presented in Table 1.

3.1. A spontaneous PKD

The rat was clinically normal. There were no abnormalities in hematology or serum chemistry parameters. At necropsy, both kidneys were moderately enlarged and when sectioned contained multiple, variably-sized (up to 3.0 mm diameter), fluid-filled spaces involving most of the renal parenchyma with predominant larger cysts in the outer medulla (Fig. 1). The liver was slightly enlarged and had an irregular surface (Fig. 2) which corresponded with spaces, similar to those seen in the kidneys, when sectioned. There were no gross abnormalities in other organs or tissues. Histologically, both the renal cortex and medulla contained numerous dilated tubules (cysts) lined by a variably squamous to cuboidal to columnar epithelium, with more predominant cystic tubular dilatation in the outer medulla (Fig. 3). Renal lesion was graded as marked, i.e., the dilated (cystic) tubules occupied approximately 90% area of the outer medulla and widely extended to the cortex. The cortex, however, was less severely (50–60% of the cortex) affected than medulla. Many of these cysts were distended by pale amphophilic fluid admixed with necrotic cellular debris, scant macrophages, and/or degenerate neutrophils. Between the cysts, some areas of the interstium were expanded by loose connective

Fig. 1. Spontaneous PKD rat. Kidneys. Multiple cysts involving most of the renal parenchyma with predominant large cysts in the outer medulla.

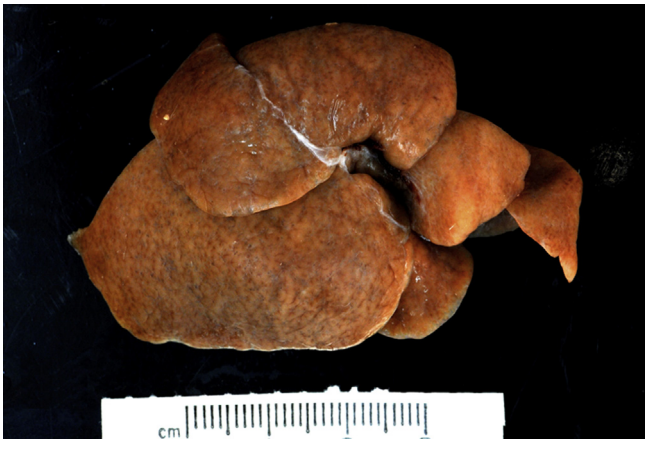

Fig. 2. Spontaneous PKD rat. Liver with granulated surface.