

## Multicystic Renal Dysplasia in a Japanese Black Bull

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**ABSTRACT.** Multicystic renal dysplasia was found in a 6-day-old Japanese black bull. Grossly, both kidneys were markedly small (2.0 × 3.5 cm) with numerous cysts ranging from 1 to 8 mm in diameter. Histopathologically, both kidneys consisted of many irregularly enlarged cysts, immature glomeruli, small ducts and anomalous stromal connective tissues containing focal persistent mesenchyme characterized by a proliferation of stellate cells with myxomatous area. These features are compatible with those of multicystic renal dysplasia in humans and other mammals.—**KEY WORDS:** bovine, multicystic renal dysplasia.

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Developmental abnormalities of the kidneys are classified generally into renal aplasia, hypoplasia, and dysplasia. In addition, disorganization or partial lack of renal tissue is known as agenesis. Among these congenital changes, renal dysplasia is disorganized development of the renal parenchyma due to anomalous differentiation and is characterized histologically by the persistence of abnormal structures consisting of cartilage, undifferentiated mesenchyme, immature collecting ductules, and abnormal lobar organization. In humans, this renal abnormality is well documented [3, 5] and there are also several reports of spontaneous renal dysplasia in domestic animals such as dogs, pigs, sheep and horses [1–2, 4, 14, 16, 18], although there are few reports of this renal condition in cattle [7]. Because of incomplete blastema and ureteral bud formation, human dysplastic kidneys are often cystic, and the most common variety may be the multicystic dysplastic kidney [4, 12], although there are only few reports of cystic renal dysplasia in domestic animals [11, 17].

In this paper we describe the morphological features of severe hypoplastic multicystic renal disease found in a 6-day-old Japanese Black bull and discuss its conformity with multicystic renal dysplasia.

**Case history:** A 6-day-old Japanese black bull showed hypoplasia of the submaxillary bone. Blood chemical examination revealed a marked increase of blood urea nitrogen (BUN 165.5 mg/dl) and creatinine (8.0 mg/dl), and a decrease of plasma calcium (4.2 mg/dl). Following the owner's decision, the animal was euthanatized by electric shock and necropsied immediately.

**Histopathology:** Representative tissue samples were fixed with methanol Carnoy's solution and 10% formalin for histopathological and immunohistochemical examinations. Paraffin sections of 4 μm thick were made and stained with hematoxylin and eosin (HE). Selected sections were also stained with alcian blue (pH 2.5), Masson's trichrome, and periodic acid-Schiff (PAS). Immunohistochemistry was performed using Envision-Polymer reagent (Dako, Carpinteria, CA, U.S.A.). As primary antibodies, mouse

monoclonal antibodies against vimentin (1:50, Dako, Denmark) and alpha-smooth muscle actin (α-SMA) (1:50, Dako, Denmark), and rabbit polyclonal antibody against keratin (prediluted, Dako, Carpinteria, CA, U.S.A.) were used. The reaction products were visualized using diaminobenzidine (Sigma, St. Louis, U.S.A.). Mayer's hematoxylin was used for counterstaining.

**Pathological findings:** At necropsy, both kidneys were yellowish and markedly small 2.0 × 3.5 cm, with numerous multiple cysts ranging from 1 to 8 mm in diameter. At the cut surface of both kidneys, the junction between the cortex and the medulla was obscured, and the enlarged cysts were filled with clear fluid (Fig. 1). The ureters and urinary bladder did not show any gross changes. In the visceral organs other than the kidneys, there were no significant gross lesions except for hypoplasia of the submaxillary bone.

Microscopically, both kidneys involved in severe dysplastic lesions throughout the cortex and medulla. The renal lesions were characterized by a large number of irregularly enlarged cysts, small ducts, proliferating connective tissue and immature glomeruli (Fig. 2). The immature glomeruli (Fig. 3) were irregularly distributed in the superficial area of both kidneys in low density. The connective tissues consisted of diffuse proliferation of small spindle-shaped cells with moderate collagen deposits and focal proliferation of stellate cells with myxomatous stroma (Fig. 4) supposed to be persistent mesenchyme. Immunohistochemically, these spindle-shaped cells were identified as fibroblasts, positive only for vimentin, and myofibroblasts or smooth muscle cells, positive for both vimentin and α-SMA. In the primitive mesenchyme, the stellate cells showed immunoreactivity for vimentin and α-SMA. The enlarged cysts were lined by two types of epithelium. Most cysts were formed by a single layer of flattened epithelial cells, which were commonly positive for both vimentin and keratin (Fig. 5. arrow). Some enlarged cysts mimicking dilated Bowman's capsules were also lined by a single layer of flattened epithelial cells, which showed intense immunoreactivity only for vimentin. Small ducts were lined mainly by a single layer of cuboidal epithelial cells. The immunoreactivity of these cells for keratin or vimentin varied in the ducts, although most cells were positive for both. In addition, some small ducts lined by pseudostratified

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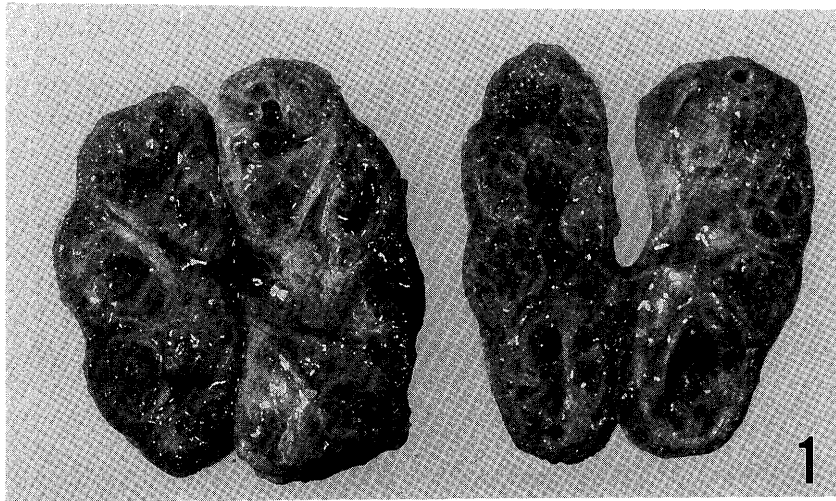


Fig. 1. Gross appearance of both kidneys which were markedly small and had numerous dilated cysts varied in size.

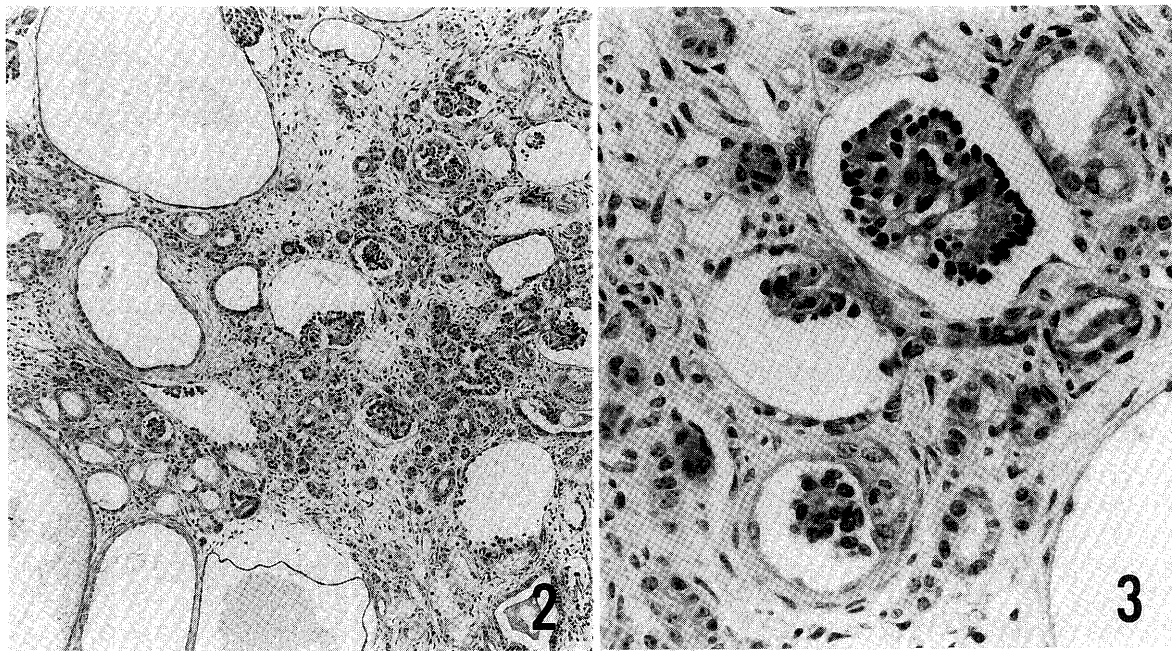


Fig. 2. Irregularly dilated cysts, atrophic glomeruli within cystic Bowman's capsules and mild proliferation of stromal connective tissue. HE stain.  $\times 50$ .

Fig. 3. Immature glomeruli. HE stain.  $\times 250$ .

columnar epithelium which were positive only for keratin, suggesting that they were primitive metanephritic ducts (Fig. 5. arrow head). There were occasional deposits of oxalate crystals in the small immature ducts. From these findings, the kidney was considered to show "multicystic renal dysplasia". In the other organs examined, there were no significant histological lesions.

The diagnosis of human renal dysplasia is based on the presence of (1) bone or cartilage in the parenchyma, (2) persistent mesenchyme, (3) fetal or immature glomeruli, (4) fetal or immature tubules, and (5) anomalous presence of

interstitial fibrous connective tissue [4-7, 11, 17]. In the present case, persistent mesenchyme, immature glomeruli and ducts, and interstitial connective tissues were important features for the diagnosis of renal dysplasia. Cystic renal diseases including polycystic kidney, which represent a heterogeneous group comprising hereditary, developmental, and acquired disorders, might be considered in the differential diagnosis. Cystic kidneys are sometimes associated with cystic bile ducts, bile ductal proliferation and pancreatic cysts. Syndromes resembling both the autosomal dominant and autosomal recessive forms of

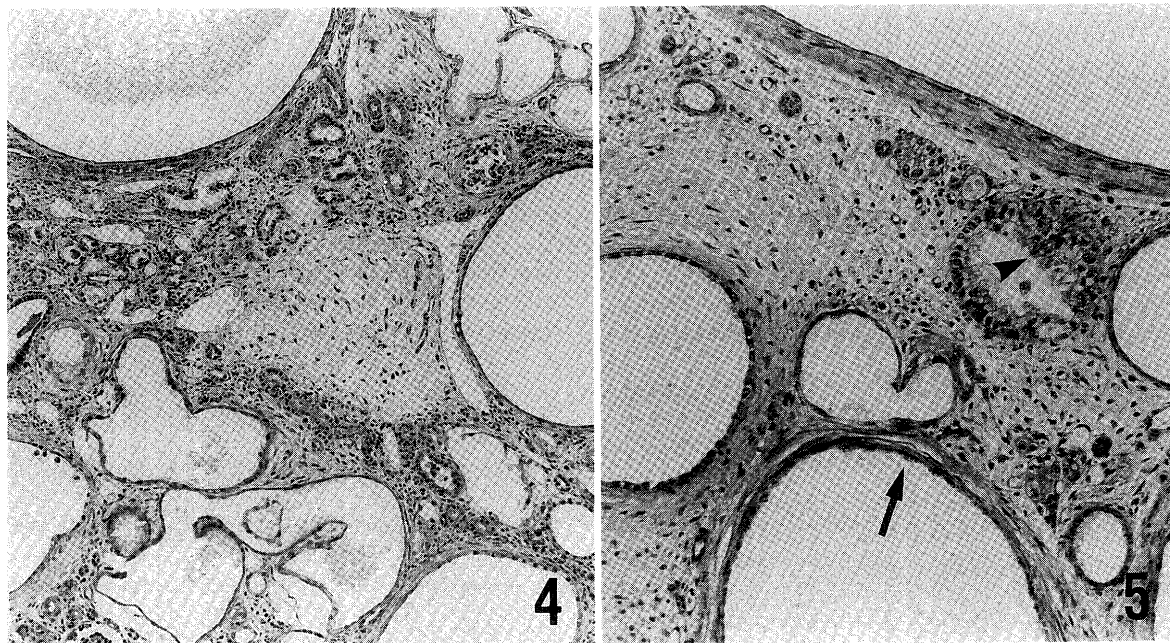


Fig. 4. A focus of primitive mesenchyme of small stellate cells with myxomatous stroma. HE stain.  $\times 60$ .

Fig. 5. Renal cyst lined by flattened epithelium (arrow) and a primitive metanephric ducts lined by pseudostratified columnar epithelium (arrow head). HE stain.  $\times 100$ .

human polycystic kidney disease have been reported in cats, pigs, lambs, horses, ferrets, and puppies [4, 10, 14–15]. Moreover, some chemicals, such as corticosteroids, diphenylamine and polychlorinated biphenols, are also known to cause cystic lesions in experimental animals [14]. There are several morphological similarities between multicystic renal dysplasia and polycystic kidney, although the major differences are the size of the kidney (dysplastic kidney may be small and/or misshapen, and cystic kidneys are commonly enlarged) and the kidney components (dysplastic kidney contains persistent mesenchyme and immature metanephric ducts). From this view point, the morphological features of the present case are mostly consistent with those of renal dysplasia.

Some authors have indicated that the presence of cysts and proliferation of interstitial fibrous connective tissue may be considered a secondary change [4, 17]. Cartilage and/or osseous nodules sometimes found in human dysplastic kidneys are thought to be rare in renal dysplasia of domestic animals, and were not recognized in this case. A lack of cartilage formation considered to be related to the early gestational age at which a kidney is obtained [7, 13]. The presence of fetal glomeruli, as well as typical tubular epithelium and fetal tubules, are the initial induction of the metanephric blastema that impedes complete differentiation [3, 11]. Primitive metanephric ducts lined by pseudostratified columnar epithelium surrounded by primitive mesenchyme and/or dysontogenic metaplasia are considered to be due to complete failure of interaction of the ureteric bud and the metanephric blastema. Several factors are proposed to cause renal dysplasia [8, 13, 19]. In

transgenic models of mouse kidney development, an alteration in the genes responsible for the branching morphogenesis of the ureteric ducts results in significant changes similar to the above abnormalities, including cystic renal dysplasia. In humans, renal dysplasia is commonly associated with extrarenal anomalies of the urogenital tract, whereas extra-renal anomalies are rarely reported in dogs [11, 17]. In addition, human familial forms of renal dysplasia such as autosomal dominant/recessive polycystic kidney disease are usually associated with multiple organ malformation. Similar syndromes have also been reported in dogs [2, 15]. In addition, there is a report of bovine renal dysplasia with multiple urogenic and large-intestinal anomalies [9]. In the present case, hypoplasia of the submaxillary bone was recognized together with renal dysplasia. Thus, some genetic embryonal abnormality was probably responsible for the pathogenesis, although there was no evidence to support the familial history. On the other hand, in several animals which have an active subcapsular nephrogenic zone at birth [14], renal dysplasia is known to arise until nephrogenic differentiation is complete. Viral infections such as bovine viral diarrhea mucosal disease virus, hypovitamin A, and physical occlusion of the ureters in fetal or neonatal animals may also result in renal dysplasia [14]. These etiologies were also possible in the present case. Since the present study is a preliminary one, it is difficult to clarify the etiology of bovine multicystic renal dysplasia, although this case revealed various morphological features of this rare bovine renal condition.

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