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A case of hydronephrosis in a CD-1 outbred mouse with associated clinicopathological findings

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Abstract

Hydronephrosis is a renal disorder characterized by dilation of the renal pelvis and calyces resulting from impaired urinary outflow, which can lead to progressive enlargement of the kidney and subsequent functional impairment. The condition may present unilaterally or bilaterally and can occur at any stage of life, including the prenatal period. This pathological condition is well-recognized in the laboratory mice and has been reported both experimentally and in spontaneous settings. The present report documents a case of spontaneous hydronephrosis in an outbred adult male CD-1 mouse maintained under standard laboratory conditions. Gross examination revealed marked enlargement of the affected kidney, while clinicopathological analyses confirmed dilation of the renal pelvis and calyces consistent with hydronephrosis. This case underscores the occurrence of spontaneous renal pathology in laboratory rodents and highlights the importance of thorough renal evaluation in research animals.

Keywords: Hydronephrosis, kidney, CD-1 mouse, renal pelvis, rodent

Introduction

Laboratory animals are indispensable to biomedical and preclinical research, with mice and rats accounting for approximately 95% of laboratory animal use. The use of healthy animals is critical for the validity of experimental outcomes, as spontaneous diseases can confound results; reduce data reliability, and compromise reproducibility. Laboratory mice commonly develop naturally occurring lesions that may mimic, mask, or exacerbate experimentally induced phenotypes. Documented background pathologies include renal, respiratory, dermatological, cardiovascular, metabolic, reproductive, endocrine, and neoplastic disorders. Notably, renal diseases are the second leading cause of mortality in laboratory mice, emphasizing the importance of careful pathological assessment in experimental studies (Nemoto *et al.*, 2024; Vigneshwar *et al.*, 2021) ^[10, 15].

Hydronephrosis is characterized by dilation of the renal pelvis and calyces due to impaired urine outflow, leading to urinary retention and progressive renal damage. In mice, spontaneous hydronephrosis occurs predominantly in certain inbred strains, with marked strain variability indicating a strong genetic component. Males are more frequently affected, often with greater involvement of the right kidney (Ninomiya *et al.*, 1999; Yoshioka *et al.*, 2016) ^[11, 16]. Although generally uncommon, spontaneous hydronephrosis has been reported more frequently in inbred strains such as C57BL/6 and DDD mice, while occurrences in outbred strains are rare, with only a single documented case in CD-1 mouse (Chandra and Frith, 1994) ^[2].

The etiology of hydronephrosis in mice is multifactorial, encompassing genetic predisposition, infection, urolithiasis, neoplasia, and congenital or acquired urinary tract abnormalities, particularly in aging animals (Springer *et al.*, 2014) ^[14]. In humans, hydronephrosis most commonly results from urinary tract obstruction caused by conditions such as calculi, neoplasms, strictures, or prostatic enlargement, while pediatric cases are often congenital, paralleling spontaneous disease in certain mouse strains. Across species, hydronephrosis is defined by progressive dilation of the renal pelvis with compression and atrophy of the renal parenchyma (Davisson *et al.*, 2015) ^[3].

Case History

At the Laboratory Animal House of Christian Medical College (CMC), Vellore, mice colonies were maintained in groups on sterilized bedding within Individually Ventilated Cages (IVCs). The animals were housed in separate rooms designated for breeding, holding, and experimental purposes. All husbandry and animal care procedures were carried out in strict compliance with the guidelines prescribed by the Committee for the Control and Supervision of Experiments on Animals (CCSEA), Govt. of India.

During routine health monitoring, a six-month-old male CD-1 mouse from the founder colony exhibited clinical signs suggestive of distress, including back arching, abdominal pressing, reduced activity, right-sided abdominal distension, decreased urination, and reduced feed and water intake. Physical examination revealed a large, soft, fluid-filled swelling in the neck region (Fig. 1). The animal was anesthetized and subjected to fine-needle aspiration biopsy; clear fluid was aspirated using a tuberculin syringe (Fig. 2).



Fig 1: Large fluid-filled lump on the neck



Fig 2: Aspiration of clear fluid using fine needle

A comprehensive health screening was undertaken, including oral swab examination, urine and fecal cultures, and serological testing, all of which were negative for bacterial, viral, and parasitic infections. Biochemical analysis revealed elevated serum parameters indicative of renal dysfunction. Considering the severity of the clinical signs and laboratory findings, the animal was humanely euthanized by carbon dioxide (CO₂) asphyxiation in accordance with ethical guidelines.

Necropsy examination revealed bilaterally enlarged kidneys. The right kidney was markedly enlarged and softer in

consistency compared to the left (Fig. 3), with dilation of the renal pelvis and thinning with atrophy of the renal parenchyma. The left kidney was also enlarged and congested. In addition, seminal vesiculitis was observed. Based on the gross pathological findings, a diagnosis of bilateral hydronephrosis was confirmed.



Fig 3: Left kidney-inflamed & congested; Right kidney-enlarged with multiple fluid filled cysts

Materials and Methods

Smears were prepared from the aspirated fluid, air-dried, fixed in methanol, and stained with Giemsa. Urine samples were aseptically collected directly from the urinary bladder following euthanasia and initially examined under low-power magnification (10×) for sediment evaluation. Further, urinalysis was performed using *Medi-Test Combi 10 VET* urine dipsticks as per the manufacturer's instructions. Blood samples were collected immediately after euthanasia via cardiac puncture. Hematological parameters were assessed using an automated blood analyzer. Serum was separated by centrifugation, and biochemical analyses, including blood urea nitrogen (BUN), creatinine, total protein, and electrolytes, were performed using an automated clinical chemistry analyzer in accordance with standard operating procedures. All values obtained were compared with established reference ranges for CD-1 mice (Serfilippi *et al.*, 2003)^[13].

Semen samples were collected immediately after euthanasia from the cauda epididymis and examined microscopically at 40× magnification to assess sperm motility. Thin smears were prepared on clean glass slides and stained with Eosin-Nigrosin for evaluation of sperm morphology and viability. The stained smears were examined under oil immersion at 100× magnification.

Tissue samples from the kidneys, urinary bladder, and seminal vesicles were collected and fixed in 10% neutral buffered formalin. The tissues were subsequently dehydrated through graded concentrations of isopropyl alcohol, cleared in xylene, embedded in paraffin wax, sectioned at 5 µm thickness, and stained with Hematoxylin and Eosin (H&E). Histopathological examination was performed using a light microscope.

Results

Giemsa-stained FNAB smears revealed the presence of numerous leukocytes, indicative of an inflammatory response. Hematological analysis demonstrated elevated total white blood cell (WBC) and platelet counts, further supporting the presence of inflammation. Reduced lymphocyte levels and decreased packed cell volume (hematocrit) were observed, suggestive of edema (Table 1). Biochemical evaluation showed increased serum

concentrations of blood urea nitrogen (BUN) and creatinine, measuring 36 mg/dL and 0.6 mg/dL, respectively. These values exceeded the established reference ranges for CD-1 male mice (BUN: 16-22 mg/dL; creatinine: 0.1-0.3 mg/dL), confirming renal dysfunction. In contrast, serum total protein and albumin levels were reduced, with values of 4.7 g/dL and 2.2 g/dL, respectively, compared with normal reference ranges (total protein: 5.4-6.4 g/dL; albumin: 3.2-3.9 g/dL), indicating hypoproteinemia. Electrolyte imbalances were also observed (Table 2). Microscopic examination of urine revealed the presence of a few red blood cells, and dipstick analysis was positive for protein, indicating proteinuria. Semen analysis demonstrated poor sperm motility (30%), a high proportion of morphologically abnormal spermatozoa (50%), and a substantial percentage of non-viable sperm (60%), confirming infertility.

Table 1: Hematological Parameters

S. No.	Analyte	Result	Reference range
1	WBC ($\times 10^3/\text{mm}^3$)	21.6	8.57-14.01
2	Lymphocytes %	33.8	37.50-85.01
3	Monocytes %	5.5	6.77-13.09
4	Neutrophils %	55.5	23.45-55.68
5	Eosinophils %	4.2	2.16-5.20
6	Basophils %	1.0	0.01-1.70
7	RBC ($\times 10^6/\text{mm}^3$)	7.29	7.31-12.27
8	Hb (g/dL)	12.3	11.9-18.4
9	HCT (%)	35.1	39.7-74.7
10	MCV (fL)	48	46.5-69
11	MCH (pg)	16.9	13.1-18
12	MCHC (g/dL)	35.1	21.3-33.9
13	PLT ($\times 10^3/\text{mm}^3$)	3863	1580-2374

Table 2: Serum Biochemical Parameters

S. No.	Analyte	Result	Reference range
1	BUN (mg/dL)	36	16-22
2	Creatinine (mg/dL)	0.6	0.1-0.3
3	Total Protein (g/dL)	4.7	5.4-6.4
4	Albumin (g/dL)	2.2	3.2-3.9
5	Sodium (meq/L)	135.2	147.9-155.2
6	Potassium (meq/L)	13.62	9.26-11.18

Histopathological analysis of kidney sections revealed loss of the tubular brush border accompanied by severe degenerative alterations in the renal tubules. Both proximal and distal tubules were markedly dilated and lined by flattened epithelial cells. Eosinophilic casts were present within the lumina of some tubules, along with mild congestion of the interstitial capillaries (Fig. 4A-C). Microscopic examination of the seminal vesicle showed numerous empty tubules which contained eosinophilic secretory material and a few exfoliated cells (Fig 4-D).

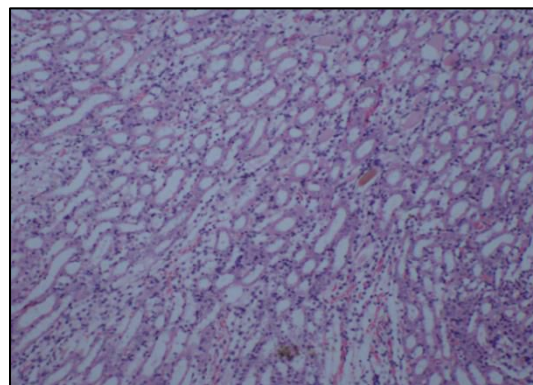


Fig 4-A: Right kidney showed diffuse, severe renal tubular dilation with eosinophilic cast

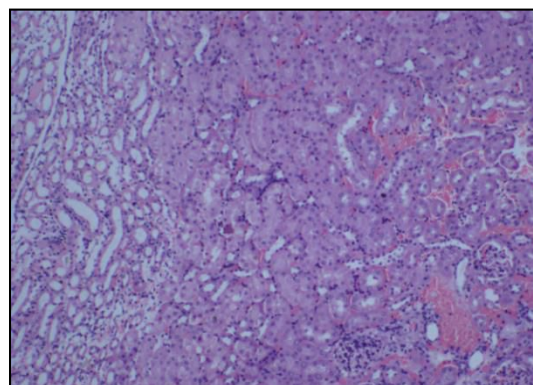


Fig 4-B: Right kidney showed dilated renal tubules on the left side, while the tubules on the right side appeared normal with haemorrhagic interstitium

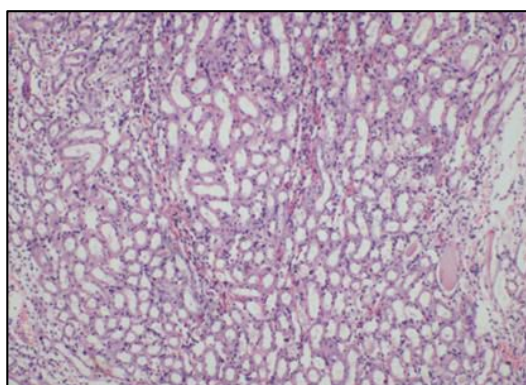


Fig 4-C: Left kidney-dilated renal tubules with degenerative alterations

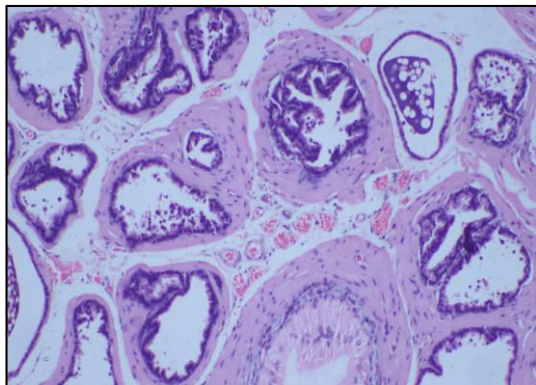


Fig 4-D: seminal vesicle showed empty tubules, and cellular degeneration

Discussion

Experimental hydronephrosis is commonly induced in animals by ureteral ligation; however, naturally occurring models are considered more desirable due to their simplicity and translational relevance. Spontaneous hydronephrosis has been reported in several inbred mouse strains, including C57BL/6 and C57BL/KsJ, as well as in B6-based congenic strains such as MRL/MpJ and B6/DBA F2, which serve as models for obstructive uropathy and developmental hydronephrosis caused by inflammatory and hyperplastic narrowing of the ureteropelvic junction. In contrast, CD-1 is an outbred mouse strain, and only a single report of spontaneous hydronephrosis has been documented to date (Chandra and Frith, 1994) ^[2], highlighting its potential value for investigating genetic and pathological associations of the condition.

Nakajima *et al.*, (1983) ^[9] classified hydronephrosis in laboratory rodents into two types: obstructive hydronephrosis secondary to identifiable urinary tract obstruction and non-obstructive hydronephrosis of unknown etiology. The present case corresponds to the latter category, as no definitive obstructive mechanism was identified, indicating the need for further investigation into its pathogenesis. Lozzio *et al.*, (1967) ^[7] described three types of macroscopic renal lesions—solitary macrocysts, hydronephrosis, and cicatricial scarring of the kidney surface—in the hereditary renal disease of Gunn rats. Similarly, Nakajima *et al.*, (1983) ^[9] reported medullary atrophy with loss of the medulla and cortical atrophy in cases of spontaneous hydronephrosis in DOD mice. Additionally, lymphocytopenia alone or in conjunction with C-reactive protein (CRP) could be a surrogate marker for reactive and obstructed renal conditions (Ali *et al.*, 2015) ^[1], these findings align with the present observations.

Previous studies have reported marked kidney damage in KK-A^y male mouse with hydronephrosis, including an enlarged renal pelvis, thinning of the cortex and medulla, shrunken glomeruli, dilated tubules, tubular epithelial degeneration, and interstitial fibrosis (Ninomiya *et al.*, 1999) ^[11]. Cortical atrophy and dilation of renal tubules and the pelvis were demonstrated as key histological features of hydronephrosis by Frazier *et al.*, (2012) ^[4]. Formation of eosinophilic crystals in the cytoplasm of hyperplastic urothelial cells has also been observed in affected mice (Ichii *et al.*, 2017; Ozaki *et al.*, 2014) ^[6, 12]. However, the timing and mechanisms underlying the initiation of inflammation and epithelial proliferation before the onset of hydronephrosis remain unclear. The histopathological

findings of the present study are consistent with these earlier reports.

Renal failure is known to impair male fertility through various spermatotoxic mechanisms including hormonal dysregulation, hypogonadism, disrupted spermatogenesis and erectile dysfunction leading to oligospermia, oligoasthenozoospermia, azoospermia or sertoli cell atrophy (Holley, 2004; Lundy and Vij, 2019) ^[5, 8]. The reproductive abnormalities observed in this study are consistent with these established mechanisms.

Conclusion

Spontaneous hydronephrosis is uncommon in mice and has been predominantly reported in genetically predisposed inbred strains such as C57BL/6 and DDD. In contrast, CD-1 is an outbred strain, suggesting that the condition in the present case was acquired rather than hereditary; however, the exact pathogenesis could not be determined. Although infectious diseases are effectively controlled in SPF facilities, systemic non-infectious conditions cannot be entirely excluded. Therefore, careful maintenance and review of pedigree records during breeder selection are recommended to reduce breeding-related complications.

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Conflict of Interest

The authors declare no conflict of interest.

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