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## Case report

# Multiple renal and liver cysts in a Siberian hybrid tiger

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## Abstract

Polycystic kidney disease (PKD) is an inherited disease commonly reported in cats, but rarely in big cats. It is associated with formation of cysts in the kidneys. This article describes the clinical, pathology and immunohistochemistry findings of PKD in a Siberian hybrid tiger. A 16-year-old female captive Siberian hybrid tiger showed inappetence, weight loss, polyuria, and polydipsia. Within six months, its body weight and hydration status were progressively declining. Although hematology parameters were normal, serum creatinine and urea levels were elevated. Ultrasonography of the kidneys showed the presence of cysts. The animal was euthanized and necropsied, revealing multiple cysts in both kidneys and liver. These samples were subjected to histopathology using routine stain, special histochemistry, and immunohistochemistry. The cysts were lined by various types of epithelial cells. Most renal tubular epithelium showed severe vacuolar degeneration, accompanied by bacterial colonies in the renal pelvis. Masson's trichrome stain demonstrated presence of mesenchymal stroma at the periphery of the cysts in the kidneys and liver. Immunohistochemistry showed different staining intensity of β-catenin, E-cadherin, and vimentin in the various parts of renal tubules, suggesting the involvement of epithelial-mesenchymal transformation. The tiger was diagnosed with PKD based on clinical and pathological examination. This is the first report of PKD in a tiger, potentially useful for future study in wildlife medicine and conservation.

**Keywords**: Chronic kidney disease, Panthera tigris, Polycystic kidney disease, Siberian hybrid tiger

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## INTRODUCTION

Cystic diseases of the kidney and liver are conditions which are characterized by formation of one or more cystic cavities. In general, formation of cysts in the kidneys are generally related to obstructive lesions, destruction of the tubular basement membrane, disturbed growth of tubular epithelial cells, abnormalities in specific membrane protein polarity, cell-matrix interactions, and imbalance ion and fluid secretion (Wilson, 2004; Silberberg et al., 2005; Igarashi and Somlo, 2007). On the other hand, formation of cysts in the liver mainly occurs due to dilatation of bile ducts as a result of defective remodeling of the embryologic ductal plate (McAloose et al., 1998; Williams et al., 2008). In humans, development of cysts in the kidneys and liver is associated with an inherited kidney disease termed as polycystic kidney disease (PKD) (Harris and Torres, 2009). PKD can be further classified into two types; autosomal dominant polycystic kidney (ADPKD) and autosomal recessive polycystic kidney disease (ARPKD) (Bergman, 2015). The former has been recorded in many species of animals especially in Persian cats, Persian-related cats, bull terriers, Nubian goats, and mice (Nauta et al., 1993; Krotec et al., 1996; Barrs et al., 2001; O'Leary et al., 2003; Schirrer et al., 2021), while the latter has been reported in West Highland White and Cairn terriers, sheep, and mice (McKenna and Carpenter, 1980; McAloose et al., 1998; Johnstone et al., 2005; Williams et al., 2008).

In general, ADPKD in cats occur due to mutation in polycystin-1 (PKD1) gene (Lyons, 2004), affecting the polycystin-1 protein that play important functions in the proliferation and differentiation of tubular epithelium, and inhibiting apoptosis of tubular epithelium. Apart from renal cysts, cats with PKD may also show multiple hepatic cysts and hepatic fibrosis (Biller et al., 1996; Eaton et al., 1997; Bosje et al., 1998, Sato et al., 2019). In big cats, case reports of PKD, or hepatic cyst, or renal cyst are extremely rare. Previous available reports are a lion with hepatic cysts but without renal cyst (Yu et al., 2019), a lion with renal and hepatic cysts (Gerhauser et al., 2009), and three jaguars with renal cysts (Hope and Deem, 2006). Other reports revealed presence of cysts in cougars, leopards, lions, and tigers that may not be severe enough to warrant the diagnosis of PKD (Newkirk et al., 2010; D'Arcy, 2018;). This article describes the clinical and pathology changes in a tiger with renal and hepatic cysts.

## CLINICAL HISTORY AND SYMPTOMS

A 16-year old female Siberian hybrid tiger (*Panthera tigris*), managed in captivity within a zoo was noticed to show signs of cachexia, inappetence, polyuria and polydipsia since May 2021. The tiger was provided a symptomatic treatment with amoxicillin and clavulanic acid (Amoxyclav 12.5 mg/kg, PO BID) and Azodyl (4 capsules PO SID) but the symptoms persisted after a week of treatment. Subsequently, the tiger was subjected to a full physical examination in June 2021 under general anesthesia. Induction was done using a combination of ketamine and detomidine at the dosage of 5 mg/kg and

0.07 mg/kg, respectively. The physical examination revealed that the animal was underweight at 102.5 kg but no other remarkable physical abnormality was found. Complete hematology did not show any abnormality, but serum biochemistry revealed elevated creatinine level of 8.21 mg/dL and high urea level of 97.76 mg/dL. Ultrasonography of the kidneys revealed no abnormality of the left kidney, but presence of a renal cyst, measuring 1.6 cm in the right kidney.

Between July and November 2021, the clinical signs worsened, warranting two more physical examinations, which were done in October and November 2021. It was found that the body weight had declined from 90 kg in October 2021 to 76 kg in November 2021, while the animal was assessed as suffering from severe dehydration. Similar to the previous hematology results, no abnormality was observed on both occasions. The creatinine level was elevated at 10.99 mg/dL in October 2021, but was not detectable in November 2021. The urea levels were elevated in October and November 2021, at 224.93 mg/dL and 129.97 mg/dL, respectively. Serum symmetric dimethylarginine (SDMA) was only measured in October 2021, measuring 50.9 µg/dL. During the physical examination in October 2021, a 2.6 mm × 50 cm urinary catheter was placed followed by collection of a urine sample. Urinalysis revealed urine specific gravity (SG) of 1.015, presence of erythrocytes, leukocytes and protein in the urine, and isolation of pure colonies of *Escherishia coli* from the urine. Ultrasonography of the kidneys was repeated in October 2021, showing multiple cysts of various sizes ranging between 0.29 cm and 2.97 cm in diameter in the right kidney, and a single cyst was observed in the left kidney (Figure 1). The tiger was treated with daily oral Azodyl and Neuroforte® throughout June and November 2021. Summary of clinical findings were presented in Table 1. Based on the clinical signs, serum biochemistry, urinalysis and ultrasonography, the tiger was suspected of PKD.

Following declining health, the tiger was euthanized in November 2021 using pentobarbital at the dosage of 150 mg/kg. Necropsy was performed immediately.

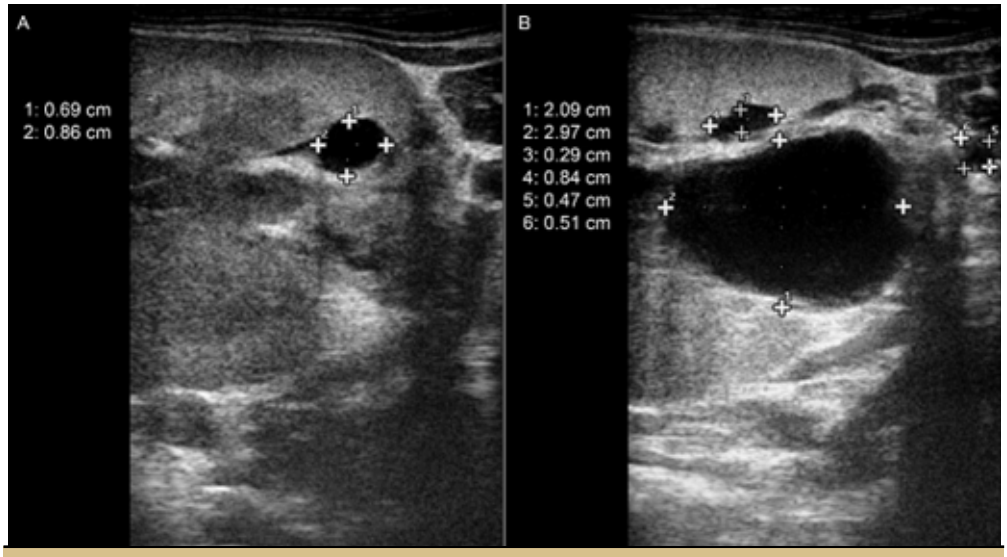


**Figure 1** Findings of ultrasonography in October 2021. (A) A single cyst measuring 0.69 cm × 0.86 cm was found in the right kidney. (B) Presence of multiple cysts of various sizes within the left kidney

**Table 1** Body weight, hydration status, serum urea, creatinine and SDMA levels, ultrasonography and urinalysis of the tiger in June, October and November 2021.

| Parameters | June 2021 | October 2021 | November 2021 |
|---|---|---|---|
| Body weight | 102.5 kg | 90.0 kg | 76.0 kg |
| Hydration status | Normal | Dehydrated | Severely dehydrated |
| Serum creatinine reference: 0.7–4.1 mg/dL (Mota et al., 2021) | 8.21 mg/dL | 10.99 mg/dL | not detectable |
| Serum urea reference: 37–114 mg/dL (Proverbio et al., 2021) | 97.76 mg/dL | 224.93 mg/dL | 129.97 mg/dL |
| Serum SDMA reference: 7.0–2.22 µg/dL (Mota et al., 2021) | not done | 50.9 µg/dL | not done |
| Ultrasonography | Right kidney: One small cyst<br>Left kidney: Normal | Right kidney: Multiple small cysts<br>Left kidney: One small cyst | not done |
| Urinalysis | not done | SG: 1.015<br>Erythrocyte: 5+<br>Leukocytes: 3+<br>Protein: 4+ | not done |

# DIAGNOSIS

## Necropsy

At necropsy, the tiger was extremely emaciated with obvious protuberances of the spinal column and pelvic bone, while the hind limbs were severely atrophied (Figure 2A). Further examination revealed a lack of subcutaneous fat, while the visceral fat was minimal. There was focal emphysema at the right caudal lung lobe while many small, soft nodules were found embedded in the entire lung parenchyma. The stomach was devoid of feed, while the antrum and pylorus of the stomach were seen with a thin layer of bile on the mucosa. Similar content, but of mucoid consistency was observed in the entire small intestine. The large intestine had well-formed, dark-colored fecal materials. The pancreas was normal. The liver was severely congested and cut sections revealed coalescing cysts of approximately 5 mm diameter. Both kidneys showed similar cystic lesions, but of slightly different severity. Bisection of the kidneys resulted in spurting of fluid. The kidneys were generally pale with pelviectasis. Yellowish material was observed adhering to the surface of the left renal pelvis, suggestive of pyelonephritis. Adhesion between the renal capsule and cortical surfaces were noted in both kidneys. Serial trimming of the kidneys revealed the presence of numerous cysts of various sizes throughout the renal cortex and medulla. The urinary bladder contained a small amount of cloudy urine with three spots of hemorrhages.

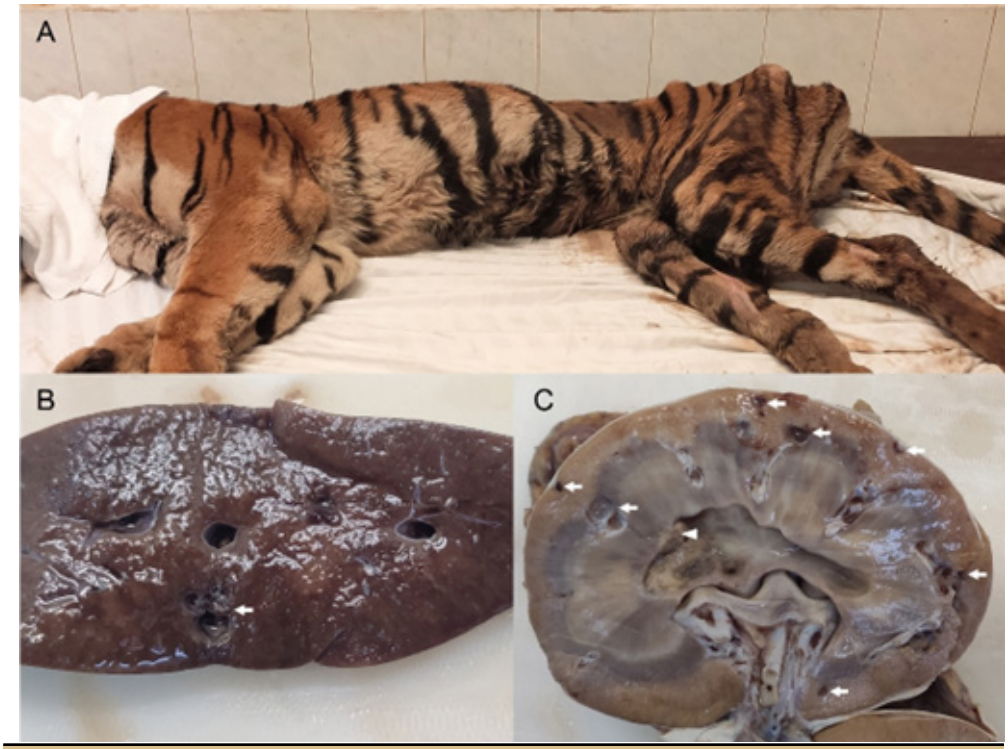


**Figure 2** Necropsy findings of a tiger with multiple kidney and liver cysts. (A) Severe emaciation with obvious bony protuberances and muscle atrophy. (B) The liver shows coalesced cysts of various sizes (arrow). (C) Presence of numerous small cyst (arrows) with pelviectasis and suppurative pyelonephritis (arrowhead) in the kidney

Samples of the lungs, liver, kidney, stomach, intestine and urinary bladder were fixed in 10% neutral-buffered formalin before they were subjected to routine tissue processing using paraffin-embedded techniques and stained with hematoxylin and eosin (HE). The liver and kidney were also subjected to special histochemistry (Masson's trichrome) and immunohistochemistry (IHC) (E-cadherin, vimentin and β-catenin). Archived samples of normal liver and kidney of an adult Malayan tiger (*Panthera tigris jacksoni*) were retrieved and were similarly subjected to special histochemistry and IHC for comparison. For IHC, direct IHC were used for all markers. The protocols for both the cystic and control tissues were similar (Hewitt et al., 2014). Following removal of paraffin wax and hydration, the tissue sections were pre-treated with ULTRA Cell Conditioning Solution (ULTRA CC1), and were incubated with the antibodies, followed by incubation in a signal amplification solution. The sections were then incubated in DAB solution for chromogenic detection prior to counter staining.

## Histopathology

The lungs revealed moderate pulmonary oedema and suppurative bronchopneumonia. The bronchopneumonia was characterised by infiltrations of neutrophils and macrophages. Pulmonary haemorrhages were mild and found scattered throughout the lung section. This was accompanied by hemosiderin-laden macrophages, erythrophagocytosis by macrophages and deposition of amyloid. In the intestine, mild infiltration of macrophages and lymphocytes were observed, but limited to the mucosal layer. A single

coalesced cyst was observed in the liver section with a few smaller cysts located immediately to its proximity (Figure 3A). The cysts are mainly lined by simple epithelia either squamous or cuboidal that were placed near each other. However, stratification was observed in few areas. Lumen of the large cyst was empty, while the smaller cysts contained erythrocytes. The liver parenchyma surrounding the cysts was mildly congested. Some of the liver sinusoids were dilated by the presence of amyloid, which was also observed surrounding most of the blood vessels of the liver (Figure 3B).

The renal cysts were lined by single cuboidal epithelium, pseudostratified columnar epithelium with micro projections, squamous or stratified cuboidal epithelium. The wall of the cyst was surrounded by a layer of fibrous tissue, and appeared filamentous when two cysts were formed next to one other (Figure 3C). Most tubular epithelium of the renal cortex showed severe vacuolar degeneration, some exhibiting cytoplasmic eosinophilia, accompanied by presence of eosinophilic cast within the tubular lumen (Figure 3D). Many renal tubules were denuded of tubular epithelial cells, while tubular atrophy and amyloid depositions in the interstitial space were observed in most areas of the renal cortex. Interstitial fibrosis as confirmed by Masson's trichrome and tubular atrophy were severe in the renal medulla. Chronic tubulonephritis was also observed, characterized by infiltrations of lymphocytes and plasma cells in the interstitial spaces. Bacterial colonies and small foci of calcification were noted in the left renal pelvis.

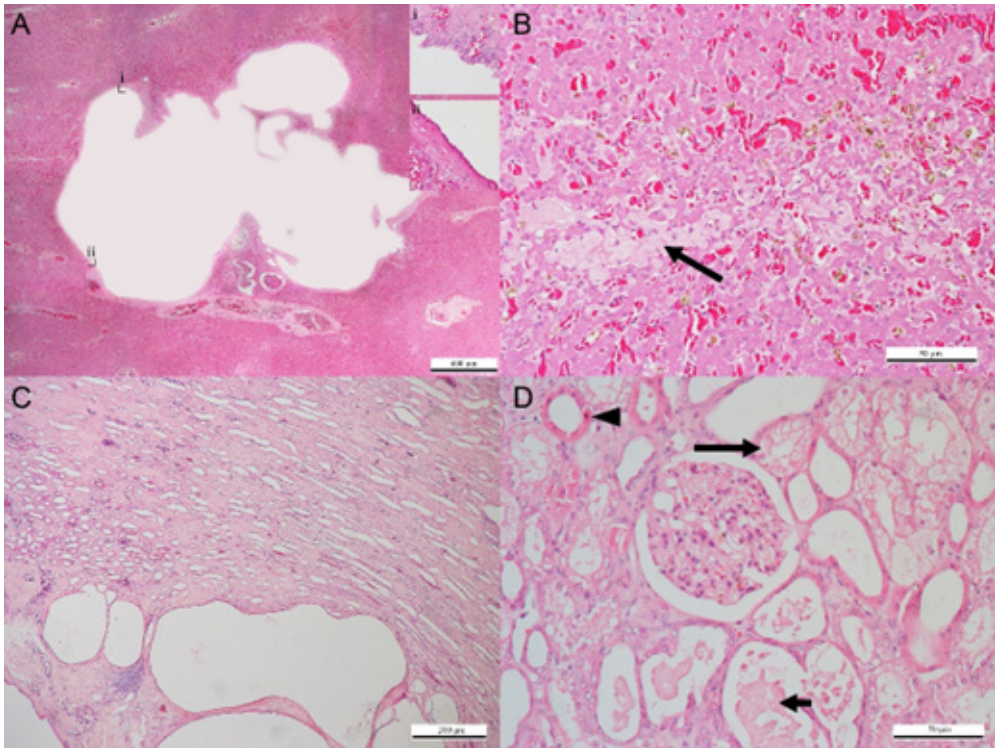


**Figure 4** Immunodetection of vimentin, E-catenin, and β-catenin in the cortex and medulla of polycystic and normal kidneys of tiger (original magnification: ×400, bar = 30 μm).

## Immunohistochemistry

Immunohistochemistry assessment was done to consider the location of staining and semiquantitative intensity of positive staining; +: weak staining; ++: moderate staining; and +++: intense staining (Conklin et al., 2013). There was intense cytoplasmic expression of vimentin in renal epithelium of all distal convoluted tubules (DCT). Only a few nuclei of the renal epithelium of DCT showed weak positive expression of vimentin. The epithelial cells of the proximal convoluted tubules (PCT) showed weak to no expression of vimentin. In the medulla, the majority of the thick segments of loop of Henle (LOH) tubular epithelium showed intense cytoplasmic expression of vimentin. Most of the interstitial areas showed expression of vimentin in moderate intensity. On the contrary, the negative control kidneys showed that only few DCT epithelial cells expressed vimentin in the cytoplasm, and all PCT epithelial cells were negative for vimentin. The epithelial cells of few thick segments of LOH expressed vimentin in either the entire cytoplasm or only limited to the basal portion of the cytoplasm, while the interstitial areas did not show expression of vimentin.

As for β-catenin, the kidneys of PKD tiger showed that the renal epithelial cells of all PCT showed intense cytoplasmic expression, while the nuclei occasionally were observed with moderate expression of β-catenin. Almost all collecting ducts showed moderate expression β-catenin. Accumulated casts in denuded tubules and the tubular epithelial cells of DCT both showed mild cytoplasmic expression of β -catenin. On the other hand, the negative control kidney showed mild basolateral expression of β-catenin in the renal epithelium lining the DCT and collecting duct. For E-cadherin, the renal tubular epithelium of PKD tiger showed intense cytoplasmic or basolateral E-cadherin expression in the PCT and thin segment of LOH, and partial and weak positivity in the thick segment of LOH. The accumulated casts in the renal medulla of the PKD tiger showed positive E-cadherin. The control tiger showed mild expression of E-cadherin in the DCT and all PCT were negative for E-cadherin. The renal medulla of the control kidney showed moderate basolateral E-cadherin expression in the collecting duct and thick segment of LOH. Summary of the IHC findings are presented in Table 2 and Figure 4.

Based on the clinical, gross, microscopic, and IHC findings, the tiger was diagnosed with PKD.

**Table 2** Summary of intensity and distribution of vimentin, β-catenin, and E-cadherin expressions in polycystic and normal kidneys of tiger.

| Markers | Polycystic kidney | | | Normal kidney | | |
|---|---|---|---|---|---|---|
| | Renal structure | Intensity | Distribution | Renal structure | Intensity | Distribution |
| Vimentin | PCT | ± | c | PCT | - | |
| | DCT | +++ | c | DCT | ± | c |
| | Thick LOH | +++ | c | Thick LOH | ± | c, b |
| | Thin LOH | - | | Thin LOH | - | |
| | Collecting duct | - | | Collecting duct | - | |
| | Interstitial | ++ | | Interstitial | - | |
| β -catenin | PCT | +++ | c, n | PCT | - | |
| | DCT | + | c | DCT | + | bl |
| | Thick LOH | - | | Thick LOH | - | |
| | Thin LOH | - | | Thin LOH | - | |
| | Collecting duct | ++ | c | Collecting duct | + | bl |
| | Interstitial | - | | Interstitial | - | |
| E-cadherin | PCT | +++ | c, bl | PCT | - | |
| | DCT | + | c, bl | DCT | + | c, bl |
| | Thick LOH | + | c, bl | Thick LOH | ++ | bl |
| | Thin LOH | +++ | bl | Thin LOH | - | bl |
| | Collecting duct | ++ | bl | Collecting duct | +++ | bl |
| | Interstitial | - | | Interstitial | - | |

PCT: proximal convoluted tubule, DCT: distal convoluted tubule, LOH: loop of Henle, b: basal, bl: basolateral, c: cytoplasmic, n: nuclear, -: negative, ±: positive in some areas and negative in some areas, +: weak staining, ++: moderate staining, +++: intense staining.

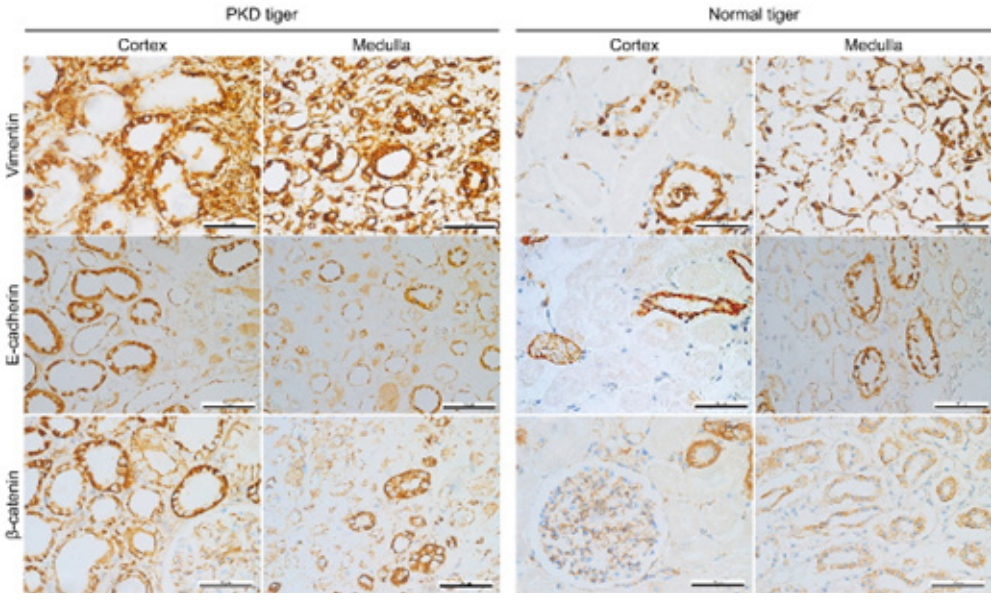


**Figure 3** Immunodetection of vimentin, E-catenin, and β-catenin in the cortex and medulla of polycystic and normal kidneys of tiger (original magnification: ×400, bar = 30 μm).

## DISCUSSION

As cysts formed in the kidneys, the functional renal parenchyma was gradually destroyed that eventually resulted in irreversible damage to renal functions (Raptis et al., 2018). This tiger showed a clinical course typical of a chronic kidney disease when the clinical signs were observed in the late stage of the disease, while multiple cysts had already been formed in the affected kidneys. The post-mortem findings of ADPKD are associated with the presence of multiple cysts of various sizes in the kidney. To a lesser extent, cysts may also be found in the liver and/or pancreas of ADPKD patients. Among the feline species, renal cysts have been reported in cats and a lion.

IHC techniques that detected vimentin, β-catenin and E-cadherin were used in this study as the technique is known to be useful in understanding ADPKD in both human and animal models (Togawa et al., 2011). Both E-cadherin and β-catenin are known to play important roles in cell-to-cell adhesion, and they are expressed especially at the basolateral aspects of normal epithelial cells (Togawa et al., 2011). Furthermore, PKD1 gene products may form a complex that contains β-catenin and E-cadherin. Histopathology and IHC examinations in this case revealed findings that were suggestive of epithelial-mesenchymal transition (EMT) of the renal tubular epithelium. Together with TGF-β, β-catenin can induce loss of cell-cell adhesion leading to a more mobile phenotype and induction of EMT characterized by expression of vimentin (Togawa et al., 2011; Basu et al., 2018). Furthermore, affected cells undergo suppression of E-cadherin that leads to release and translocation of β-catenin into the cytoplasm and subsequently into the nucleus. This eventually triggers the expression of EMT-inducing transcription factors (Ghahhari and Babashah, 2015). In this case, many of the cells of renal epithelium showed cytoplasmic expression of E-cadherin and β-catenin, and some epithelial cells lining the PCT were observed with β-catenin expression in their nuclei. This, along with the extensive expression of vimentin suggest EMT in the pathogenesis of cyst formation in this case. Based on vimentin expression, the DCT and the thick segment of LOH are likely more susceptible to cyst formation. Therefore, in our case the urine was mildly concentrated (SG 1.015) due to compromised architecture of the LOH and DCT, which are important in concentrating urine production. However, due to the limited number of samples, conclusive remarks may not be possible.

In humans and cats, the gold standard for the diagnosis of PKD involves confirmation of PKD-1 gene mutation. Alternatively, PKD can be diagnosed based on pathological examination, which has been shown to be reliable due to the dominant nature of this mutation (Biller et al., 1996; Helps et al., 2007). Such an approach was used in this case as confirmation of PKD-1 gene mutation was not available. Considering the scarcity of documented cases of cystic renal and/or hepatic diseases in big cats, further studies pertaining to PKD in big cats are highly warranted. As many species of big cats including tiger and lion are listed as vulnerable or endangered according to the IUCN Red List, conservation and breeding efforts of these species should go hand-in-hand with the advancement of disease diagnosis. As ADPKD is a heritable disease, apart from genetic diversity (Kelly, 2013), it is important to select parents or populations that do not carry mutation in the PKD1 gene to ensure successful and sustainable conservation efforts for big cats.

## CONCLUSIONS

This is the first report of multiple renal and liver cysts consistent with PKD in a tiger. The gross and histopathology lesions are in agreement with the previously reported PKD in lions and in domestic cats. IHC suggests EMT as a mechanism in the development of these cysts. Further research should be conducted to understand the role of PKD1 gene in PKD in big cats.

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## AUTHOR CONTRIBUTIONS

Charisha Fraser involved in data curation, investigation, and writing (original draft). Atiqah Zulhisam involved in investigation, and writing (original draft). Mohd Noor Akmal involved in investigation, and writing (original draft). Mohd Zamri-Saad involved in conceptualization, and writing (review and editing). Annas Salleh involved in conceptualization, investigation, writing (original draft), writing (review and editing), and resources.

## REFERENCES

Barrs, V.R., Gunew, M., Foster, S.F., Beatty, J.A., Malik, R., 2001. Prevalence of autosomal dominant polycystic kidney disease in Persian cats and related-breeds in Sydney and Brisbane. Aust. Vet. J. 79(4), 257-259.

Basu, S., Cheriyamundath, S., Ben-Ze'ev, A., 2018. Cell–cell adhesion: linking Wnt/β-catenin signaling with partial EMT and stemness traits in tumorigenesis. F1000Res. 7(F1000 Faculty Rev), 1488.

Bergmann, C., 2015. ARPKD and early manifestations of ADPKD: the original polycystic kidney disease and phenocopies. Pediatr. Nephrol. 30(1), 15-30.

Biller, D.S., DiBartola, S.P., Eaton, K.A., Pflueger, S., Wellman, M.L., Radin, M.J., 1996. Inheritance of polycystic kidney disease in Persian cats. J. Hered. 87(1), 1-5.

Bosje, J.T., van den Ingh, T.S., van der Linde-Sipman, J.S., 1998. Polycystic kidney and liver disease in cats. Vet. Q. 20(4), 136-139.

Conklin, C.M., Craddock, K.J., Have, C., Laskin, J., Couture, C., Ionescu, D.N., 2013. Immunohistochemistry is a reliable screening tool for identification of ALK rearrangement in non–small-cell lung carcinoma and is antibody dependent. J. Thorac. Oncol. 8(1), 45-51.

D'Arcy, R., 2018. Chronic kidney disease in non-domestic felids in Australian zoos (Doctoral Thesis). The University of Sydney.

Eaton, K.A., Biller, D.S., DiBartola, S.P., Radin, M.J., Wellman, M.L., 1997.Autosomal dominant polycystic kidney disease in Persian and Persian-cross cats. Vet. Pathol. 34(2), 117–126.

Gerhauser, I., Philipp, U., Distl, O., Beineke, A. 2009. Multiple cyst formation in the liver and kidneys of a lion (Panthera leo): a case of polycystic kidney disease?. Eur. J. Wildl. Res. 55(4), 433-437.

Ghahhari, N.M., Babashah, S., 2015. Interplay between microRNAs and WNT/β-catenin signalling pathway regulates epithe-lial–mesenchymal transition in cancer. Eur. J. Cancer. 51(12), 1638-1649.

Harris, P.C., Torres, V.E., 2009. Polycystic kidney disease. Annu. Rev. Med. 60, 321-337.

Helps, C., Tasker, S., Harley, R., 2007. Correlation of the feline PKD1 genetic mutation with cases of PKD diagnosed by pathological examination. Exp. Mol. Pathol. 83(2), 264-268.

Hewitt, S.M., Baskin, D.G., Frevert, C.W., Stahl, W.L., Rosa-Molinar, E., 2014. Controls for immunohistochemistry: the Histochemical Society's standards of practice for validation of immunohistochemical assays. J. Histochem. Cytochem. 62(10), 693-697.

Hope, K, Deem, S.L., 2006. Retrospective study of morbidity and mortality of captive jaguars (Panthera onca) in North America: 1982–2002. Zoo. Biol. 25(6), 501-512.

Igarashi, P., Somlo, S., 2007. Polycystic kidney disease. J. Am. Soc. Nephrol. 18(5), 1371-1373.

Johnstone, A.C., Davidson, B.I., Roe, A.R., Eccles, M.R., Jolly, R.D., 2005. Congenital polycystic kidney disease in lambs. N. Z. Vet. J. 53(5), 307–314.

Kelly, P., Stack, D., Harley, J., 2013. A review of the proposed reintroduction program for the far eastern leopard (Panthera pardus orientalis) and the role of conservation organizations, veterinarians, and zoos. Top. Companion. Anim. Med. 28(4), 163-166.

Krotec, K., Meyer, B.S., Freeman, W., Hamir, A.N., 1996. Congenital cystic disease of the liver, pancreas, and kidney in a Nu-bian goat (Capra hircus). Vet. Pathol. 33(6), 708-710.

Lyons, L.A., 2004. Feline polycystic kidney disease mutation identified in PKD1. J. Am. Soc. Nephrol. 15(10), 2548–2555.

McAloose, D., Casal, M., Patterson, D.F., Dambach, D.M., 1998. Polycystic kidney and liver disease in two related West High-land white terrier litters. Vet. Pathol. 35, 77–81.

McKenna, S.C., Carpenter, J.L., 1980. Polycystic disease of the kidney and liver in the Cairn Terrier. Vet. Pathol. 17, 436–442.

Mota, S.M., Brandão, J., Guthrie, A., 2021. Comparison of blood symmetric dimethylarginine and creatinine as endogenous markers of kidney function in captive tigers (Panthera tigris). J. Zoo. Wildl. Med. 52(2), 628-637.

Nauta, J., Ozawa, Y., Sweeney, W.E., Rutledge, J.C., Avner, E.D., 1993. Renal and biliary abnormalities in a new murine model of autosomal recessive polycystic kidney disease. Pediatr. Nephrol. 7, 163–172.

Newkirk, K.M., Newman, S.J., White, L.A., Rohrbach, B.W., Ramsay, E.C., 2010. Renal lesions of nondomestic felids. Vet. Pathol. 48, 698–705.

O'Leary, C.A., Atwell, R.B., Laing, N.G., 2003. No disease-associated mutations found in the coding sequence of the canine polycystic kidney disease gene 1 in Bull Terriers with polycystic kidney disease. Anim. Genet. 34, 358-361.

Proverbio, D., Perego, R., Baggiani, L., Ravasio, G., Giambellini, D., Spada, E., 2021. Haematological and biochemical refer-ence values in healthy captive tigers (Panthera tigris). Animals. 11(12), 3440.

Raptis, V., Loutradis, C., Sarafidis, P.A, 2018. Renal injury progression in autosomal dominant polycystic kidney disease: a look beyond the cysts. Nephrol. Dial. Transplant. 33(11), 1887-1895.

Sato, R., Uchida, N., Kawana, Y., Tozuka, M., Kobayashi, S., Hanyu, N., Konno, Y., Iguchi, A., Yamasaki, Y., Kuramochi, K., Yamasaki, M., 2019. Epidemiological evaluation of cats associated with feline polycystic kidney disease caused by the fe-line PKD1 genetic mutation in Japan. J. Vet. Med. Sci. 81(7), 1006–1011.

Schirrer, L., Marín-García, P.J., Llobat, L., 2021. Feline polycystic kidney disease: an update. Vet. Sci. 8(11), 269.

Silberberg, M., Charron, A.J., Bacallao, R., Wandinger-Ness, A., 2005. Mispolarization of desmosomal proteins and altered intercellular adhesion in autosomal dominant polycystic kidney disease. Am. J. Physiol. Renal. Physiol. 288, F1153–F1163.

Togawa, H., Nakanishi, K., Mukaiyama, H., Hama, T., Shima, Y., Sako, M., Miyajima, M., Nozu, K., Nishii, K., Nagao, S., Takahashi, H., Iijima, K., Yoshikawa, N., 2011. Epithelial-to-mesenchymal transition in cyst lining epithelial cells in an orthologous PCK rat model of autosomal-recessive polycystic kidney disease. Am. J. Physiol. Renal Physiol. 300(2), F511-F520.

Williams, S.S., Cobo-Stark, P., James, L.R., Somlo, S., Igarashi, P., 2008. Kidney cysts, pancreatic cysts, and biliary disease in a mouse model of autosomal recessive polycystic kidney disease. Pediatr. Nephrol. 23, 733–741.

Wilson, P.D., 2004. Polycystic kidney disease: new understanding in the pathogenesis. Int. J. Biochem. Cell. Biol. 36, 1868–1873.

Yu, Y., Shumway, K.L., Matheson, J.S., Edwards, M.E., Kline, T.L., Lyons, L.A., 2019. Kidney and cystic volume imaging for disease presentation and progression in the cat autosomal dominant polycystic kidney disease large animal model. BMC Nephrol. 20, 259.

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