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Urocystitis, pyelonephritis, renal papillary necrosis and chronic tubulointerstitial disease causing chronic renal insufficiency in a Siberian tiger (*Panthera tigris altaica*): a case report

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ABSTRACT: The present case report describes a case of chronic renal failure characterised by renal medullary fibrosis and renal papillary necrosis in a male Siberian tiger (*Panthera tigris altaica*). A 12-year-old male Siberian tiger presented with depression, anorexia and weight loss. Blood urea nitrogen (> 50.4 mmol/l) and ammonia (71.7 µmol/l) were increased, suggesting chronic renal failure and uraemia. The tiger died secondary to gastric haemorrhage. At necropsy, the kidneys had yellow lesions in the medulla and renal papillae and petechiae in the cortex. The stomach had multiple mucosal ulcers and haemorrhage. Microscopically, marked renal medullary fibrosis and renal papillary necrosis were observed with tubular atrophy, degeneration, coagulative necrosis, calcification and chronic inflammatory cell infiltration. The renal cortex showed moderate interstitial inflammation. The urinary bladder exhibited epithelial desquamation and submucosal fibrosis. The tiger was diagnosed with chronic renal failure secondary to renal papillary necrosis and medullary fibrosis.

Keywords: chronic renal failure; emesis; gastric ulcer; papillary necrosis; renal fibrosis; uraemia; feline

Chronic kidney disease, defined as prolonged structural or functional abnormalities of the kidneys, is a common cause of death in Felidae (Lawson et al. 2015). Twelve percent of domestic cats had evidence of chronic kidney disease on necropsy (Taugner et al. 1996), the prevalence has been described to increase with age (Bartlett et al. 2010; Lawson et al. 2015). In wild felids, including cheetahs, leopards, lions and tigers, renal lesions that could cause chronic kidney disease have been reported (Munson et al. 2005; Newkirk et al. 2011; Junginger et al. 2015; Brown et al. 2016; Stenvinkel et al. 2018). Amyloidosis, bacterial pyelonephritis, renal dysplasia, nephrolithiasis, lymphoma and polycystic kidney disease are causes of chronic kidney disease in domestic cats (Brown et al. 2016). In exotic felids, amyloidosis, glomerulonephritis, glomerulosclerosis, interstitial nephritis and pyelitis have been identified as causes of chronic kidney disease (Newkirk et al. 2011; Junginger et al. 2015). Although renal papillary necrosis, characterised by renal fibrosis, leads to chronic renal failure in humans, a significant association between renal papillary necrosis, renal fibrosis and chronic renal failure has not been identified in veterinary medicine. Renal papillary necrosis with degenera-

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tive renal lesions has been reported in exotic felids (Wolf et al. 1991; Corpa et al. 2005; Newkirk et al. 2011); however, histopathological evidence of severe papillary necrosis with extensive medullary fibrosis leading to chronic renal failure has not been documented in tigers (*Panthera tigris*). Here, we report the first case of chronic kidney disease associated with renal papillary necrosis and medullary fibrosis in a Siberian tiger (*Panthera tigris altaica*).

Case description

A 12-year-old, unneutered, male Siberian tiger usually fed with chicken meat was presented to the Veterinary Medical Teaching Hospital at the College of Veterinary Medicine, Kyungpook National University (Daegu City, Republic of Korea) with anorexia, depression and weight loss. The tiger had been transferred from a local zoo to the Korean national arboretum eight days earlier. For blood examination, the tiger was mildly sedated using intramuscular administration of ketamine and whole blood was collected. For fluid therapy, isotonic fluid with 5% glucose was infused. Blood chemistry showed elevated levels of blood urea nitrogen (> 50.4 mmol/l; reference range: 6.8–12.2), ammonia (71.7 μmol/l) and creatinine (1697.3 μmol/l; reference range: 70.7–194.5). Complete blood count results showed an increased level of red blood cells (16.1×10^6/μl; reference range: 5.6–8.8) and slightly elevated haematocrit (52%; reference range: 31.8–49.2) (Table 1). The tiger was diagnosed with severe renal failure, developed haematemesis and died. Post-mortem examination was performed at the Department of Veterinary Pathology, Kyungpook National University.

At necropsy, the tiger was severely emaciated with multiple ulcerations on the oral mucosa. There were no other external lesions. The stomach was enlarged and filled with dark blood (Figure 1A). Multiple deep ulcerations and multifocal white calcified lesions were identified on the gastric mucosa (Figure 1B). The small and large intestinal mucosa were hyperaemic and congested. The rectum was filled with melena. The liver was intact, and the gall bladder was enlarged and filled with bile. The heart and pericardial sac were normal apart from mild petechiae in the endocardium. Multifocal mild haemorrhages, congestion and emphysema were noted in the lungs. The spleen was pale and

Table 1. Complete blood count and blood chemistry values of the tiger

Clinical parameter	Value	Reference interval
White blood cells ($\times 10^3$/ul)	11.9	5.1–21.1
Red blood cells ($\times 10^6$/ul)	16.1	5.6–8.8
Haemoglobin (g/l)	170	112–164
Haematocrit (%)	52	31.8–49.2
Mean cell volume (fl)	32.3	50.7–62.7
Mean cell haemoglobin (pg)	10.6	8.5–32.0
Mean cell haemoglobin concentration (g/l)	327	313–371
Total protein (g/l)	78	67–90
Albumin ($\times 10^3$/ul)	3.5	2.9–4.3
Total bilirubin (μmol/l)	10.26	0.0–6.8
Aspartate aminotransferase (U/l)	28	14.5–43.0
Alanine aminotransferase (U/l)	72	18.8–98.7
Glucose (mmol/l)	9.8	1.9–12.8
Alkaline phosphatase (U/l)	46	3–57
Inorganic phosphorus (mmol/l)	4.4	0.7–1.8
Na (mEq/l)	146	151–159
K (mEq/l)	4.7	3.0–4.5
Cl (mEq/l)	114	113–123
Blood urea nitrogen (mmol/l)	> 50.4	6.8–12.2
Creatinine (μmol/l)	1697.3	70.7–194.5
Cholesterol (mmol/l)	8.1	1.6–7.9
NH_3 (μmol/l)	71.7	

atrophied. The kidneys were yellow-tan in colour, atrophied, with an irregular surface and tight attachment of the renal capsule (Figure 1C). The inner cut surface of the kidney showed markedly yellow medullary lesions spreading from the inner medulla to the renal pyramid and yellow inflammatory exudates in the renal pelvis. These lesions are compatible with pyelitis (Figure 1D).

Representative tissue samples of organs were fixed in 10% neutral buffered formalin, routinely processed, embedded in paraffin wax, and the blocks were cut at 4 μm thickness. The sections were stained with haematoxylin and eosin, Masson's trichrome stain and Gram stain. Microscopically, the renal medulla was replaced by fibrous tissue. Tubular atrophy, tubular epithelial cell desquamation, necrosis and infiltration with chronic inflammatory cells were noted (Figures 2A and 2B). Moderate interstitial fibrosis characterised by infiltration of chronic inflammatory cells, tubular atrophy and an increased number of mesangial cells in the glomeruli were noted in the renal cortex

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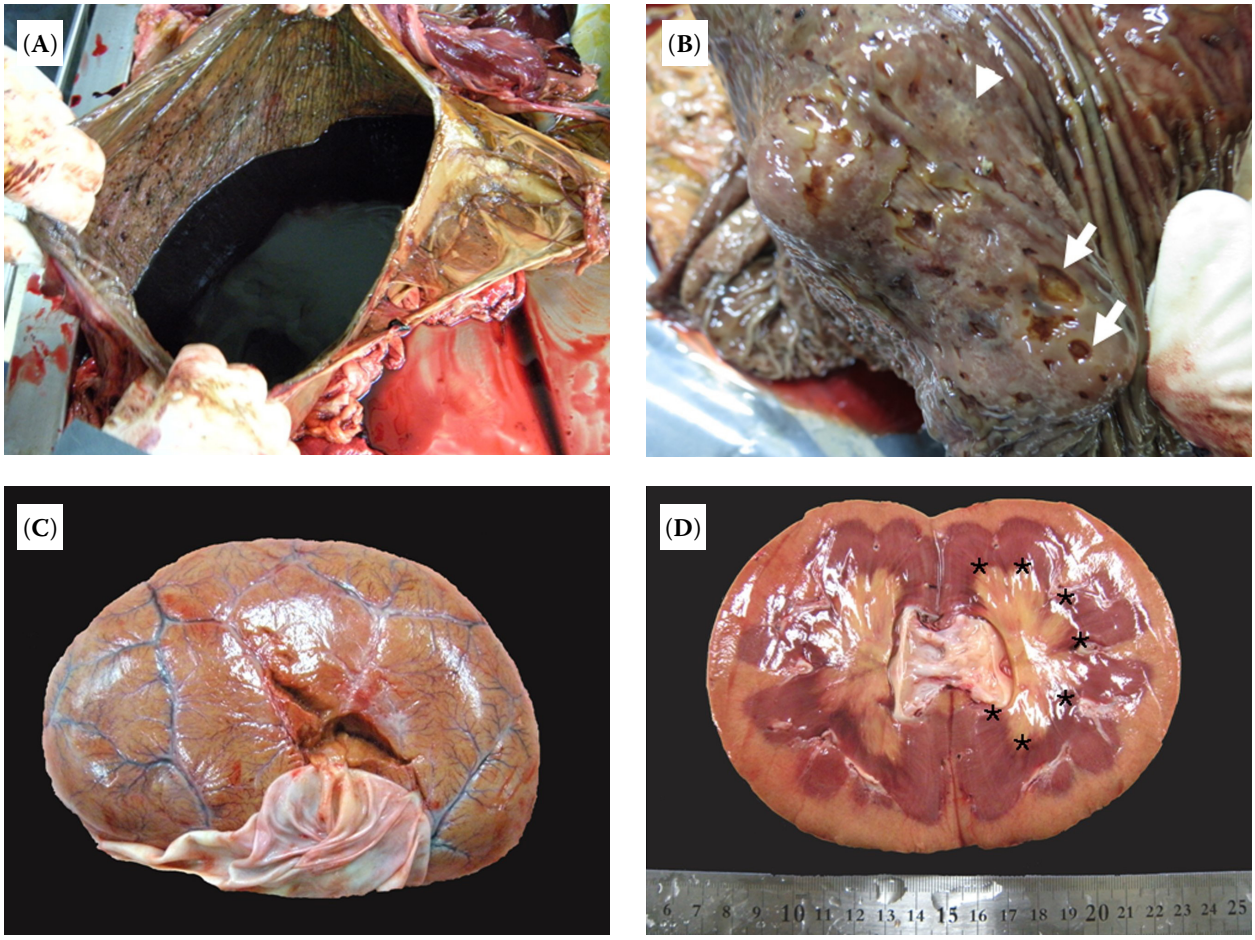

Figure 1. Kidney and stomach of a 12-year-old male Siberian tiger. (**A**) Enlarged stomach filled with dark blood. (**B**) Multiple gastric ulcerations (arrows) and multifocal white calcified lesions (arrow head). (**C**) Atrophied kidney with irregular surface and tight attachment of renal capsule. (**D**) The cut surface of the kidney with yellow papillary necrosis and medullary fibrosis (outlined by asterisks)

(Figures 2C and 2D). Multifocal calcification and calculi were observed in some tubules. The renal papilla was necrotic with homogeneous eosinophilic coagulative necrosis characterised by ghost-like tubules and dilated collecting ducts filled with desquamated necrotic epithelial cells (Figures 2E and 2F). The urinary bladder showed epithelial cell desquamation and hyperplasia of the submucosa characteristic of chronic cystitis (Figures 3A and 3B). Gram-positive bacteria, surrounded by inflammatory cells, were observed in the renal medullary tubules (Figure 3C). Ulcerations, mucosal calcification, and ruptured submucosal blood vessels resulting in haemorrhage were observed in the stomach. The lungs had oedema in the alveolar spaces, congestion and emphysematous lesions. Mild cardiac muscle fibrosis, especially around vessels, was noted.

DISCUSSION AND CONCLUSIONS

Chronic kidney disease is common in domestic cats, with a prevalence range of 1.6% to 31% (Polzin et al. 2005; Newkirk et al. 2011). Non-domestic Felidae families have a chronic kidney disease prevalence of 74% (Newkirk et al. 2011; Junginger et al. 2015). Chronic kidney disease in felids can result from high intake of red meat, polycystic kidney disease, renal amyloidosis, renal dysplasia, renal lymphoma or bacterial pyelonephritis (Brown et al. 2016; Stenvinkel et al. 2018). Although the aetiology of feline chronic kidney disease is heterogeneous, most cases involve non-specific renal lesions, including chronic tubulointerstitial inflammation and fibrosis (Chakrabarti et al. 2013).

The most common renal lesion in exotic felids (tigers, lions, cougars, leopards, snow leopards,

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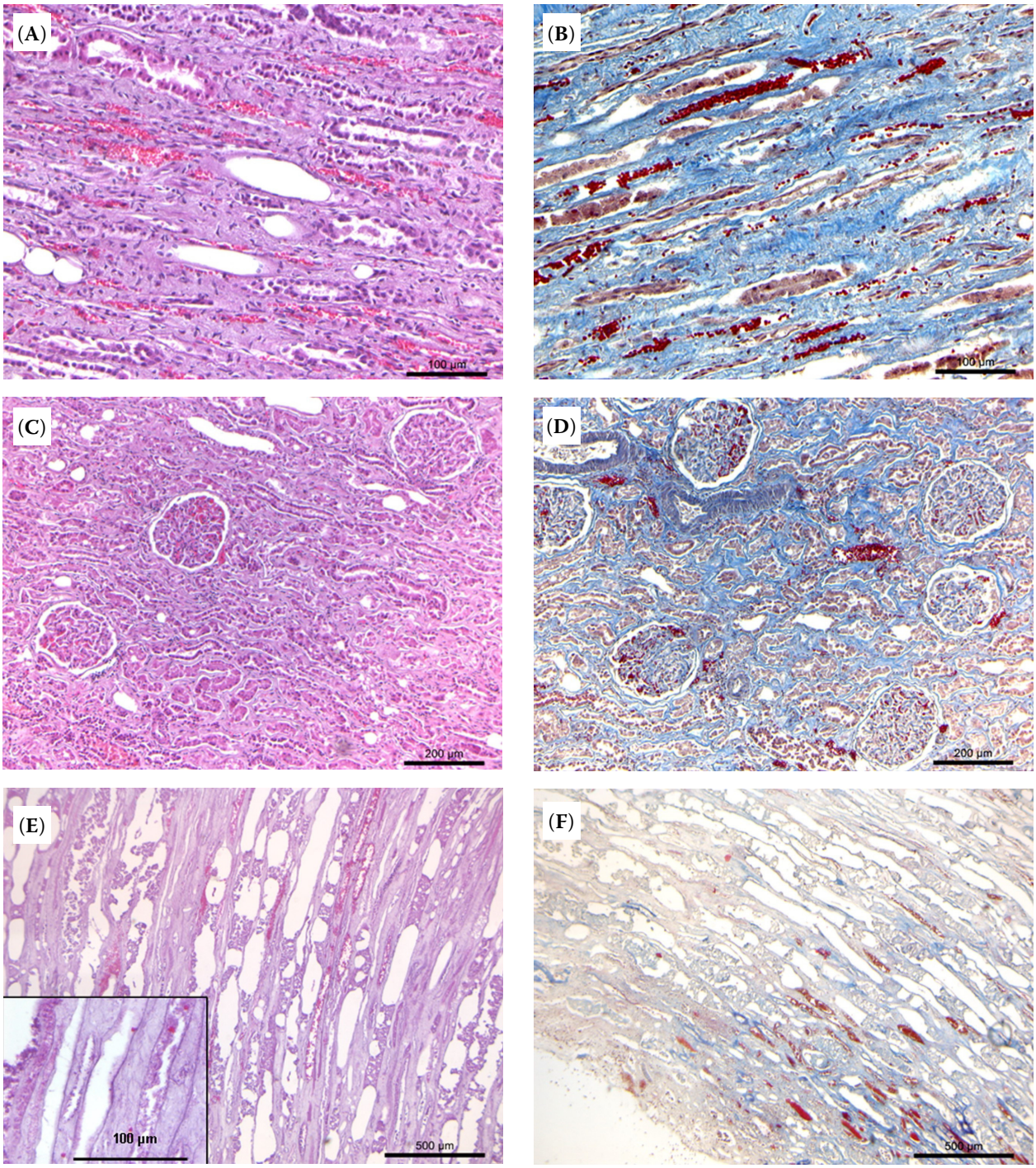

Figure 2. Representative photomicrographs of the renal medulla (**A**, **B**), cortex (**C**, **D**) and papillae (**E**, **F**). Sections **A**, **C** and **E** are stained with haematoxylin and eosin; **B**, **D** and **F** are stained with Masson's trichrome stain. (**A** and **B**) Renal medulla with fibrosis, tubular atrophy and desquamation of necrotic epithelium. Bar = 100 µm. (**C** and **D**) Renal cortex showing moderate interstitial fibrosis with tubular atrophy and increased number of mesangial cells in glomeruli. Bar = 200 µm. (**E** and **F**) Renal papilla showing extensive coagulative necrosis of dilated collecting ducts filled with desquamated necrotic epithelial debris. Bar = 500 µm. Inset, Bar = 100 µm

clouded leopards, Canadian lynx, ocelots, bobcats, cheetahs, jaguar) is tubulointerstitial nephritis (51%; 26 of 50) (Newkirk et al. 2011). Interestingly, lymphocytic interstitial nephritis was the most commonly observed renal lesion (36%; 9 of 25) in tigers (Newkirk et al. 2011). In the present case,

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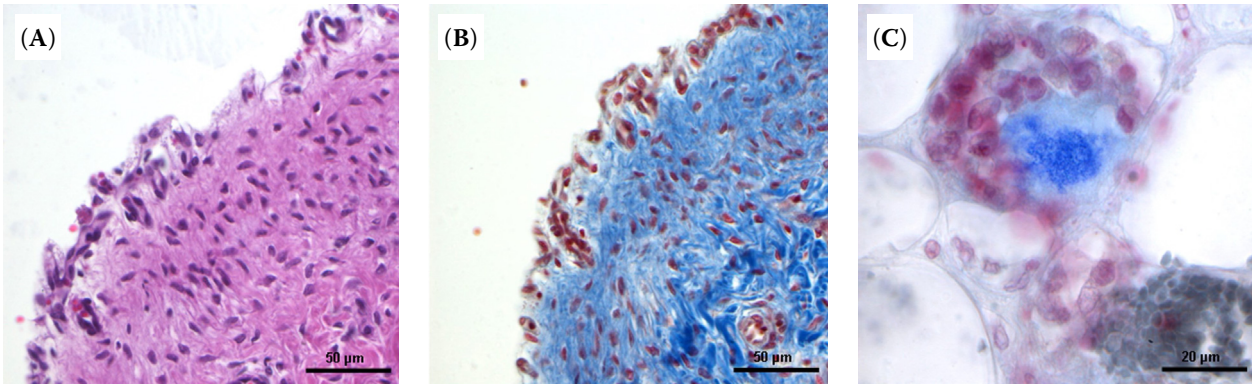

Figure 3. Representative photomicrographs of the urinary bladder mucosa and Gram stain of the renal medulla. (**A** and **B**) Urinary bladder mucosa showing desquamation of transitional epithelium and mucosal fibrosis. (**A**) Haematoxylin and eosin stain. Bar = 50 µm. (**B**) Masson's trichrome stain. Bar = 50 µm. (**C**) Gram-positive bacteria in the renal medullary tubules surrounded by inflammatory cells. Gram stain. Bar = 20 µm

the tiger had tubulointerstitial nephritis characterized by tubular atrophy, tubular epithelial cell desquamation, chronic inflammatory cell infiltration and severe medullary fibrosis extending into the cortex. Typically, severe renal papillary necrosis is accompanied by interstitial nephritis and severe renal fibrosis, suggesting an association between renal papillary necrosis and medullary fibrosis.

Renal papillary necrosis characterised by necrosis of the inner medulla is associated with coagulative necrosis of the renal papillae and medullary pyramids (Wolf et al. 1991). Although the pathogenesis of renal papillary necrosis is controversial, it is thought to be primarily caused by ischaemic injury due to vasoconstriction (Corpa et al. 2005). Ischaemia can be caused by dehydration, overuse of non-steroidal anti-inflammatory drugs (NSAIDs), analgesic nephropathy, urinary tract infection or pyelitis (Wolf et al. 1991; Corpa et al. 2005).

Glomerular or medullary amyloidosis in cats, dogs and cattle may result in renal papillary necrosis (Breshears and Confer 2017). In humans, diabetes mellitus is the most common cause of renal papillary necrosis. Sickle cell haemoglobinopathy, chronic pyelitis, urinary tract obstruction or infection and long-term use of NSAIDs are associated with renal papillary necrosis (Geller and de Campos 2013). In exotic felids, renal papillary necrosis is most commonly associated with NSAID toxicosis or dehydration and occasionally with pyelitis (Newkirk et al. 2011). In the present case, amyloidosis was not observed after Congo Red staining, and there were no clinical records of NSAID use or dehydration. However, the tiger had pyelitis and chronic cystitis characterised by fibrotic changes and desquamation of the mucosa. Moreover, Gram-positive bacteria were observed in the renal papillae, medullae and urinary bladder. There was no evidence of urinary tract obstruction. These findings suggest that the renal papillary necrosis was the result of previous pyelonephritis due to ascending bacterial infection. Although the present case has histological features similar to analgesic nephropathy in humans, this tiger had severe medullary fibrosis extending to the cortex, suggesting chronic and repetitive injury. The tiger had been anesthetised twice for transportation nine days before death and one day before death for fluid therapy. However, it is unlikely that anaesthesia induced or exacerbated papillary necrosis in this case. Instead, we suggest that renal papillary necrosis and renal medullary fibrosis were initiated by an ascending bacterial infection that progressed to pyelitis. Chronic repeated infections resulted in chronic renal failure and uraemia. The tiger died from hypovolemic shock due to massive gastric haemorrhage from uremic gastric ulcers.

Renal papillary necrosis has been reported in tigers (Wolf et al. 1991; Corpa et al. 2005; Newkirk et al. 2011); however, there was no reported case of renal papillary necrosis with severe medullary fibrosis. Moreover, our case suggests an association between medullary fibrosis and bacterial pyelitis causing papillary necrosis. A single case of bacterial pyelonephritis in a Siberian tiger has been reported in Korea (Jee et al. 2007). Pathological findings including deep medullary necrosis; neutrophilic, lymphocytic and plasmacytic infiltration; the presence of macrophages and mild fibrosis

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(Jee et al. 2007), suggest that had the animal lived longer, chronic kidney failure may have occurred. In humans, mild chronic papillary necrosis results in end-stage chronic kidney disease and chronic renal failure (Segasothy et al. 1994). The present case provides insight into the association between renal papillary necrosis and medullary fibrosis in *Panthera tigris altaica*. Marked renal papillary necrosis and medullary fibrosis were observed, which were more severe than those reported in other cases in *Panthera tigris*. There was histopathological evidence, including chronic cystitis and Gram-positive bacteria in the renal medullae, papilla and urinary bladder, suggestive of ascending bacterial pyelitis. The tiger also exhibited evidence of uraemia, including multi-focal gastric ulcers and diffuse calcification of the gastric mucosa.

With respect to the high prevalence of renal diseases in felids, many studies reported that high protein intake, especially of red meat, might result in an increased burden of chronic renal failure through high intake of sodium chloride, saturated fats, prooxidative effects of haem iron and so on (Stenvinkel et al. 2018). However, more precise effects of other protein sources such as chicken, egg or fish on renal function in felids remained to be elucidated. Thus, we assume that the high protein intake of the tiger might have exacerbated the renal lesions but were not the main cause in the present case.

To the authors' knowledge, this is the first reported case of chronic renal failure due to renal papillary necrosis and severe medullary fibrosis in *Panthera tigris altaica*. The present case can provide valuable information for the diagnosis of chronic kidney disease in *Panthera tigris*.

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