Case Report

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Fanconi syndrome with hepatorenal karyomegaly in a young Sphynx cat

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Abstract

Case summary A 3-year-old male neutered Sphynx cat was referred for history of chronically increased liver enzymes and lower urinary tract signs that were first reported when the cat was 5 months old. Urine metabolic profile revealed increased amino aciduria and glucosuria despite normoglycemia, suggesting Fanconi syndrome. Urine sodium dodecyl sulfate-polyacrylamide gel electrophoresis revealed a banding pattern suggestive of primary tubular damage. Serial blood work showed non-regenerative normocytic normochromic anemia, persistently elevated liver enzymes, worsening azotemia and progressive hyperchloremic metabolic acidosis. Ultrasound revealed irregular kidneys and bilaterally hyperechoic cortices and medullae with a loss of normal corticomedullary distinction. Laparoscopic kidney biopsy revealed a moderate-to-severe chronic interstitial fibrosis with chronic lymphoplasmacytic inflammation, tubular degeneration and atrophy, mild glomerulosclerosis and mild large vascular amyloidosis. Tubular epithelial cell karyomegaly was multifocally evident throughout the kidney. The liver had moderate diffuse zone 1 hepatocellular atrophy, periportal fibrosis, biliary hyperplasia, mild perisinusoidal amyloidosis and hepatocyte karyomegaly in zones 2 and 3. The patient continued to decline and developed polyuria, polydipsia, lethargy and hyporexia irrespective of rigorous management, which failed to curtail the progressive anemia and azotemia. The patient was euthanized 8 months from the onset of clinical signs.

Relevance and novel information Fanconi syndrome in cats is a rare condition, with most reports occurring secondary to chlorambucil treatment. This is the first known case of Fanconi syndrome occurring with concurrent hepatorenal epithelial karyomegaly in a young Sphynx cat.

Keywords: Proteinuria; glucosuria; amino aciduria; renal; kidneys; proximal tubular defect; Fanconi; karyomegaly

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Case description

A 3-year-old male neutered Sphynx cat was referred for a history of progressively elevated liver enzymes, predominantly alanine aminotransferase and persistent glucosuria despite normoglycemia for several months. The patient had had lower urinary tract signs (pollakiuria) when 5 months old and underwent perineal urethrostomy at the age of 1.5 years. Lower urinary tract signs (LUTS) persisted but resolved after therapy with polysulfated glycosaminoglycan (5 mg/kg twice weekly for 4 weeks then once weekly; Adequan; Luitpold Animal Health). Polysulfated glycosaminoglycan was tapered down to once every 3 months as LUTS were less

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Table 1 Bloodwork and urinalysis findings at initial presentation until time of euthanasia

Parameter	10/2020	01/2021	RI	02/2021*	04/2021*	RI
HCT/PCV	36	X	32–47%	22.3	19.6	28.2–52.7%
MCV	48	X	40–52 fl	50	51	39–56 fl
MCHC	33	X	32–36 g/dl	32.3	32.1	28.5–37.8 g/dl
Reticulocytes	19.6	X	0–50 10^3/µl	4	4	3–50 K/µl
Glucose	115	97	68–140 mg/dl	109	140	72–175 mg/dl
BUN	32	**44**	18–35 mg/dl	**70**	**114**	16–37 mg/dl
Creatinine	1.2	**1.9**	0.8–2.4 mg/dl	**1.9**	**3.1**	0.9–2.3 mg/dl
SDMA	X	X	0–14 µg/dl	**20**	**35**	0–14 µg/dl
Phosphorus	4.9	**7.0**	3–6 mg/dl	6.0	**9.5**	2.9–6.3 mg/dl
Calcium	9.6	10.0	9.2–11.1 mg/dl	10.2	9.6	8.2–11.2 mg/dl
Potassium	**3.7**	**3.3**	3.9–5.6 mEQ/l	4.9	4.0	3.7–5.2 mmol/l
Chloride	**127**	**126**	110–119 mEQ/l	120	124	114–126 mmol/l
Total protein	**5.7**	6.7	6.3–8 g/dl	6.9	6.6	6.3–8.8 g/dl
Albumin	3.3	3.6	3.1–4.4 g/dl	2.8	2.9	2.6–3.9 g/dl
Total bilirubin	0.0	0.0	0–0.1 mg/dl	0.1	0.1	0–0.2 mg/dl
ALP	50	33	10–80 IU/l	25	34	12–59 IU/l
ALT	347	125	30–140 IU/l	79	147	27–158 IU/l
AST	81	35	15–45 IU/l	32	38	16–67 IU/l
GGT	0	0	0–0.5 IU/l			
pH (venous blood gas)	**7.240**	**7.091**	7.33–7.44	X	**7.250**	7.33–7.44
Bicarbonate	**12.8**	**11.0**	15–24 mEQ/l	X	**12.2**	24.0–28.0 mEQ/l
USG	1.043	1.026		1.020	1.014	
pH (urine)	6	6		7.0	6.5	
Protein	**1+**	**2+**		**1+**	**Trace**	
Glucose	**2+**	**3+**		**3+**	**2+**	
WBCs	None	None		0–2	0–2	
Bacteria	None	None		None	None	

Abnormal findings are highlighted in bold – note that creatinine values are highlighted according to the International Renal Interest Society (IRIS) guidelines. Note the reported different RIs as parameters were performed at two different hospitals. Bloodwork post-surgery is indicated by an asterisk (*). Missing values were not available from referring blood work

RI = reference interval; HCT/PCV = hematocrit/packed cell volume; MCV = mean cell volume; MCHC = mean cell hemoglobin concentration; BUN = blood urea nitrogen; SDMA = symmetric dimethylarginine; ALP = allaline phosphatase; ALT = alanine transaminase; AST = aspartate aminotransferase; GGT = gamma-glutamyl transferase; USG = urine specific gravity; WBCs = white blood cells; X = data not available

frequent. Multiple urinalyses showed proteinuria, glucosuria (despite normoglycemia) and no bacteriuria, although one previous urine culture (cystocentesis) grew *Staphylococcus chromogenes* (10–50 k/cfu), which was treated with cefovecin (8 mg/kg SC once; Convenia; Zoetis). The patient was referred 2 months later; physical examination revealed a grade III/VI parasternal heart murmur but was otherwise normal.

Hematology was unremarkable at that visit. A point-of-care ELISA for feline leukemia virus antigen and feline immunodeficiency virus antibody (SNAP FeLV/FIV; IDEXX Laboratories) was negative. A summary of serial biochemical findings is provided in Table 1. Venous blood gas revealed hyperchloremic metabolic acidosis. Urinalysis showed urine specific gravity (USG) of 1.043, pH 6, 1+ protein and 2+ glucose. Urine culture was negative and urine protein:creatinine ratio (UPC) was 0.51. Leptospirosis real-time PCR on urine sample was negative and *Leptospira* species microscopic agglutination test for six serovars did not detect any antibodies.

Abdominal ultrasound revealed irregular kidneys with loss of corticomedullary distinction. Urine metabolic testing at PennGen Laboratories was negative for ketones and cystine but revealed increased amino aciduria, adipic acid and glucosuria, suggesting Fanconi syndrome (FS). Polysulfated glycosaminoglycan was discontinued at this time; however, recheck urinalysis showed persistent glucosuria (despite normoglycemia) and proteinuria.

Three months later, laparoscopic liver and kidney biopsies were obtained. Venous blood gas showed worsening hyperchloremic metabolic acidosis. Urinalysis showed a USG of 1.026, pH 6, 2+ protein and 3+ glucose. Serum cobalamin, folate, trypsin-like immunoreactivity and feline pancreatic lipase immunoreactivity were within the reference intervals (RIs). The coagulation panel

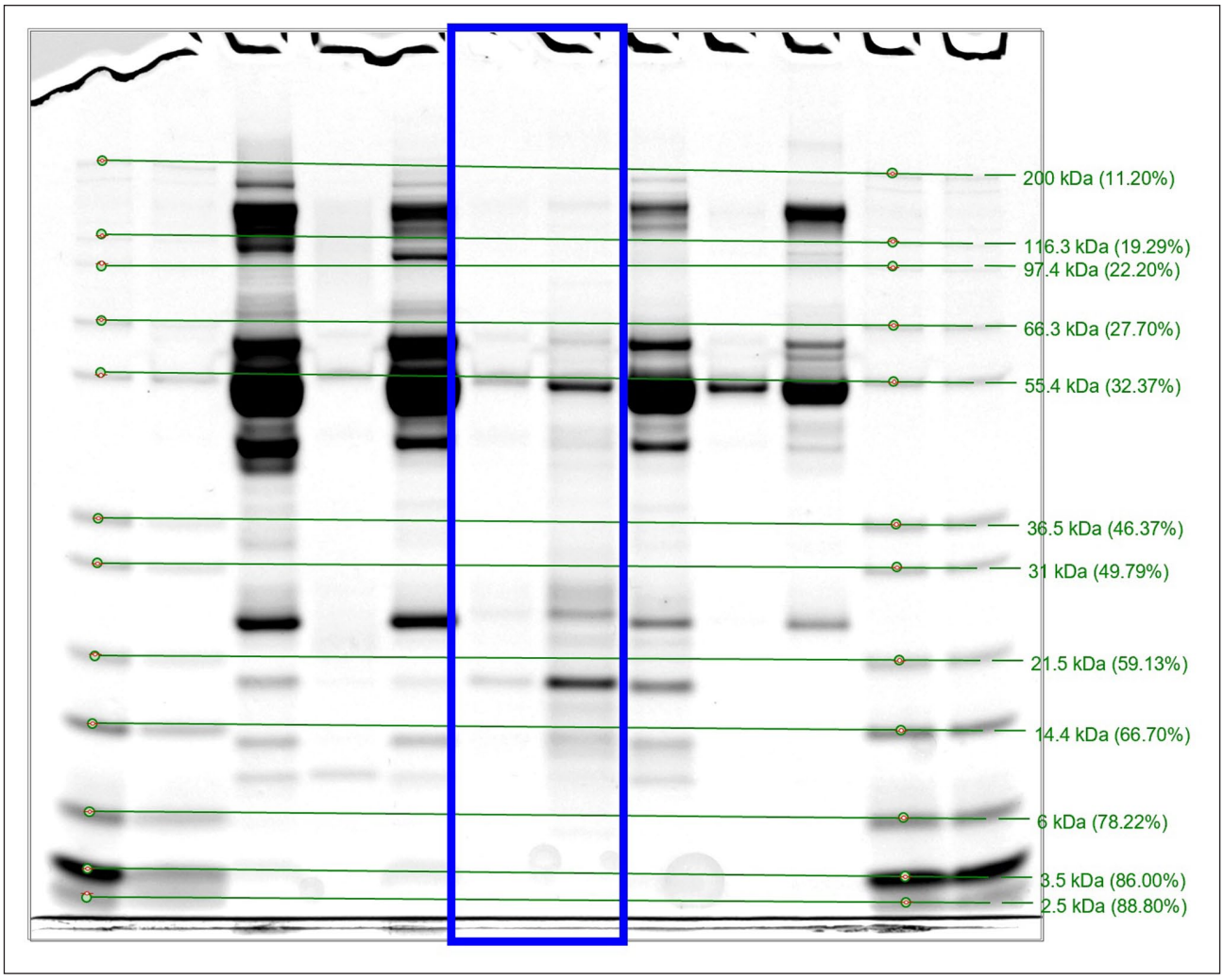

Figure 1 Urine sodium dodecyl sulfate-polyacrylamide gel electrophoresis showing patient's urine sample in the two lanes outlined in blue. In both lanes, there was an increased number and intensity of intermediate and low molecular weight proteins (tubular loss) without a corresponding increase in high molecular weight proteins (glomerular loss). The two lanes represent urine loaded based on the specific gravity of the urine (left lane) and the maximum amount of urine that could be loaded (right lane). The urine was maximally loaded due to the mild degree of proteinuria present. Lanes 1, 2, 11 and 12 are a molecular weight standard

revealed increased fibrinogen 263 (relapse incidence 124–170 mg/dl) but clotting times (prothrombin time and partial thromboplastin time) and antithrombin III were all within RIs and fine-needle aspiration of the left kidney showed marked tubular cell dysplasia. Urine sodium dodecyl sulfate-polyacrylamide gel-electrophoresis (SDS-PAGE) was suggestive of primary mild-to-moderate tubular damage without concurrent glomerular damage (Figure 1).

Laparoscopic biopsies of the right kidney, liver and small intestine were obtained. Histopathology of the kidney revealed tubular injury characterized by tubular degeneration and mild multifocal necrosis. There was marked karyomegaly of the tubular epithelium with tubular atrophy elsewhere, mild-to-moderate chronic lymphoplasmacytic and histiocytic interstitial nephritis, and replacement fibrosis. Further histopathological analysis of the kidney was also performed at the Ohio State Renal Pathology Laboratory; immunofluorescence with IgG, IgM, IgA and lambda light chain were conducted with no evidence of glomerular immune-complex deposition. Global sclerosis, mild segmental effacement of podocyte foot processes and moderate interstitial fibrosis with interstitial and intrahistiocytic lipid was documented on transmission electron microscopy (TEM). Tubular abnormalities included loss of apical brush border and detachment of the epithelium from the basement membrane. Liver histopathology revealed moderate diffuse zone 1 hepatocellular atrophy, periportal fibrosis, biliary hyperplasia and karyomegaly in zones 2 and 3. Interrupted bands of amyloid were seen in the

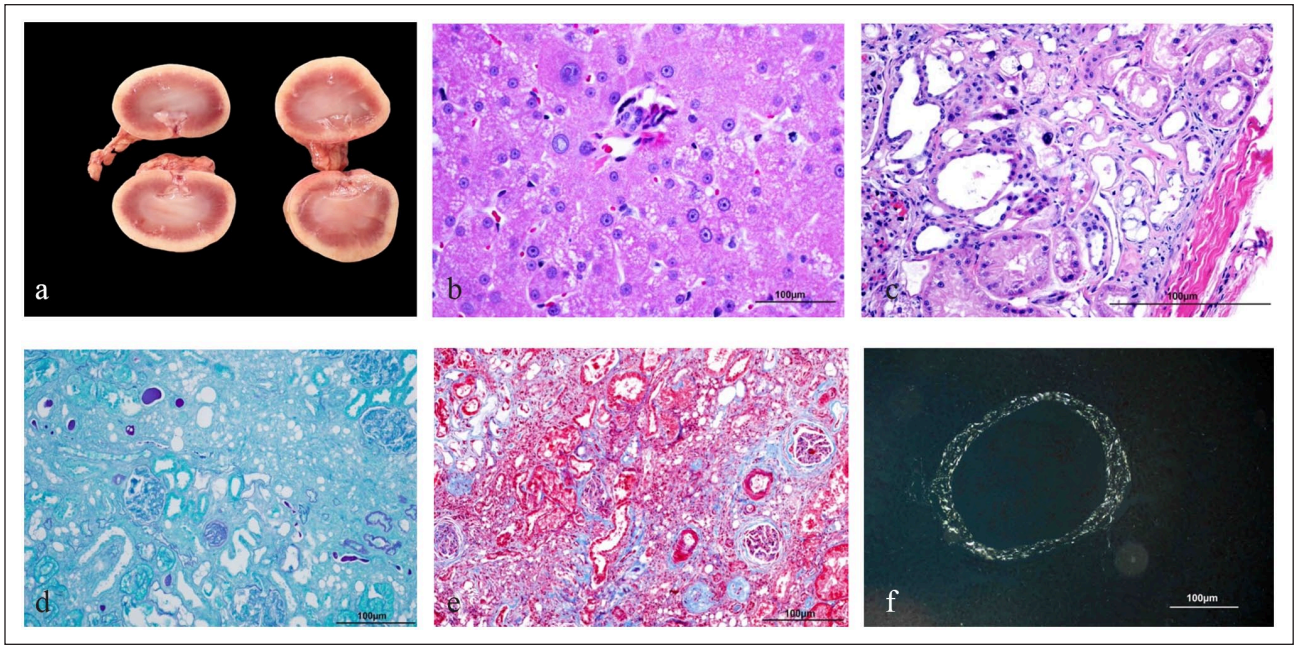

Figure 2 (a) Gross image of kidneys: the kidneys were bilaterally small and pale with a mildly irregular capsular surface. (b) Kidney (hematoxylin and eosin [H&E]): lymphoplasmacytic inflammation associated with glomeruli and tubules with evidence of damaged and ectatic tubules. Markedly thickened Bowman's capsule with glomerular effacement by eosinophilic hyalinization (glomerulosclerosis). (c) Liver (H&E): diffusely and moderately atrophic zone 1 hepatocytes dissociated and separated by congested and edematous sinusoids. Hepatocyte nuclei enlargement (up to 15 µm) with pseudo inclusions (karyomegalic cells). (d) Kidney (periodic acid–Schiff [PAS]): PAS positive intracytoplasmic droplets and tubular luminal casts. (e) Kidney (Masson's trichrome [MTS]): MTS highlighted the extensive interstitial fibrosis. (f) Liver (Congo red): Congo red highlighted amyloidosis of vascular walls in the kidney and liver

Disse space. Histopathology of the small intestines revealed a mild lymphoplasmacytic enteritis with rare crypt dilation and mild mucosal fibrosis.

After surgery, the patient developed worsening hyperchloremic metabolic acidosis and hypernatremia that improved with intravenous fluids and bicarbonate therapy. The patient was discharged 3 days post-surgery with sodium bicarbonate (1 mEq/kg PO q12h; compounded), K citrate (50 mg/kg PO q12h; compounded), maropitant citrate (1 mg/kg PO q24h; Cerenia; Zoetis), mirtazapine (1.87 mg PO q48h; compounded) and pradofloxacin (7.5 mg/kg PO q24h; Veraflox, Bayer Healthcare) while pending liver culture. Two weeks later, bloodwork showed a non-regenerative normocytic normochromic anemia with a hematocrit (HCT) of 22.3% (RI 28.2–52.7%). Serum chemistry results are shown in Table 1. Urinalysis showed a USG of 1.020, pH 7, 1+ protein and 3+ glucose and UPC of 2.4.

Three months later, the patient declined, despite the increased dosage of sodium bicarbonate (1 mEq/kg PO q8h), subcutaneous fluids and aluminum hydroxide (90mg/kg PO q12h). The patient became polyuric and polydipsic, lethargic and hyporexic. The patient remained anemic (HCT 19.6%). Recheck serum chemistry results are shown in Table 1. Urinalysis showed a USG of 1.014, pH 6.5, trace protein, 2+ glucose and a UPC of 1.3. Venous blood gas showed persistent metabolic acidosis pH 7.255 (RI 7.33–7.44) and low bicarbonate 12.2 (RI 24.0–28.0 mEQ/l). Two weeks later, the patient was euthanized owing to progressive decline and poor quality of life. On post-mortem examination, the kidneys were bilaterally small with mild capsular undulation. All other organs appeared grossly normal. Histopathology of the kidneys revealed severe chronic, multifocal interstitial fibrosis with tubular degeneration and atrophy, glomerulosclerosis, multifocal interstitial lymphoplasmacytic nephritis, amyloidosis and tubular epithelial cell karyomegaly. The liver revealed moderate diffuse zone 1 hepatocellular atrophy, periportal fibrosis, biliary hyperplasia and hepatocytic karyomegaly. No microorganisms were identified with periodic acid–Schiff or Grocott methenamine silver staining. Congo red staining revealed amyloidosis that was confined to the vascular walls in the kidney and liver (Figure 2).

Discussion

This report describes a case of FS in a young Sphynx cat with concurrent hepatorenal karyomegaly, a syndrome that has not been previously reported in cats. Congenital and acquired FS has been described in dogs,[1–6] with a familial form reported in Basenjis,[1,7] but only acquired FS

has been recently reported in cats secondary to chlorambucil use.[8] Although renal tubular karyomegaly is commonly associated with FS in dogs and cats, to our knowledge, concurrent hepatocyte karyomegaly has not been reported in FS in either species, whether congenital or acquired. Renal karyomegaly has been previously documented in humans with Fanconi anemia-associated nuclease 1 (FAN1) mutations.[9] In humans, FAN1 mutations are associated with karyomegalic interstitial nephritis due to an inadequate DNA repair mechanism,[9] and hepatic karyomegaly and elevated liver enzymes have been observed in those patients.[9–11] In FAN1-deficient mice, karyomegaly was evident in both kidneys and liver, as in this case.[12] A mutation in the *FAN1* gene has also been identified in Basenjis with FS, a commonly affected breed.[13] Histopathology of FS typically includes interstitial fibrosis, tubular atrophy and karyomegaly of the tubular epithelium mirroring the renal lesions in this cat.[14] Karyomegaly of the renal tubular epithelium has been associated with various experimental toxicoses, including 1-cyano-3,4-epithiobutane, 1-cyano-2-hydroxy-3,4-epithiobutane, alkali-treated soya protein, lysinoalanine, hexachlorobutadiene, lead and aflatoxins.[15] Hepatic karyomegaly is a well-described entity in various domestic species secondary to toxic insults including microcystin, aflatoxins and pyrrolizidine alkaloids due to increased DNA replication and inhibition of mitosis (DNA adducts). Paired hepatic and renal karyomegaly secondary to toxicosis has not been described in veterinary literature. Another feature noted on TEM was detachment of the epithelium from the basement membrane, which is related to the renal injury stemming from chronic anemic perfusion and concurrent inflammation, rather than a unique feature of Fanconi's syndrome. This finding can indicate acute kidney injury or necrosis, and rare single cell necrosis was noted histologically on the postmortem samples correlating to this finding.

In FS, a dysfunction of the proximal tubule results in abnormal excretion of glucose, amino acids, uric acid, ions and electrolytes.[16,17] Acquired FS has also been reported secondary to other medications (eg, gentamicin). Infectious and systemic diseases (eg, leptospirosis, copper-associated chronic hepatitis), jerky pet treats and toxins (eg, ethylene glycol), among other causes,[2,4–6,18] have also been reported. The patient was fed commercial diets without any exposure to jerky treats and had no previous treatment with chlorambucil or known exposure to nephrotoxic substances such as lilies or ethylene glycol. The patient was previously receiving polysulfated glycosaminoglycan for suspected idiopathic cystitis and, even though there are currently no reports of this causing FS in cats or dogs, the FS could have been induced by the polysulfated glycosaminoglycan. Additionally, discontinuation of this medication for multiple months did not resolve these clinical abnormalities.

Systemic and infectious diseases such as leptospirosis, copper-associated chronic hepatitis, primary endocrinopathies (particularly hypoparathyroidism), renal amyloidosis and multiple myelomas have also been suggested to cause FS in human and several animal species.[4–6,19] In this patient, leptospirosis and other potential non-infectious diseases were ruled out via histopathology of kidneys and liver at the time of biopsy and terminally at post-mortem examination. Special stains did not highlight any infectious organisms in the liver or kidneys; however, this does not completely rule out infectious agents as triggers for the disease process. FS in this case was confirmed with urine metabolic testing, which showed mild amino aciduria and glucosuria. Immunofluorescence and TEM analysis did not reveal significant glomerular lesions that would account for the clinical proteinuria. Copper accumulation was not evident within the liver with copper staining. Additionally, copper quantification of the liver was within our institution's reference range, at 174 ppm (RI 150–180 ppm) and copper quantification of the kidney was <134 ppm (assumed normal, no published copper concentration range available for the feline kidney). The patient declined despite supportive care with a progressive anemia, azotemia and hyperphosphatemia and was euthanized 8 months after the onset of clinical signs due to progressive worsening of polyuria, polydipsia, lethargy and hyporexia. The anemia was likely secondary to decreased production of erythropoietin from the kidneys or secondary to chronic disease/inflammation. Interestingly, the liver enzymes were within the RI despite progressing azotemia; however, the cause for the normalization of liver values is unknown but could have been related to discontinuation of polysulfated glycosaminoglycan. In dogs, liver enzyme elevation has not been reported after administration of the recommended dose of polysulfated glycosaminoglycan; however, polysulfated glycosaminoglycan is metabolized by liver and excreted by kidneys and no safety studies have been completed in cats. In dogs, there are reports of multiorgan dysfunction syndrome and acute liver and kidney toxicity secondary to overdose of joint supplements containing glucosamine;[20,21] however, these patients presented with acute clinical signs, while the patient in this case report showed chronically progressing clinical signs. There has also been a report of polyuria and polydipsia in a dog associated with increased doses of glucosamine supplement for osteoarthritis (500–1000 mg/day).[22] Despite no studies reporting development of FS owing to polysulfated glycosaminoglycan, it cannot be completely ruled out in this patient; however, given the progression of the azotemia despite no administration of polysulfated glycosaminoglycan for several months makes it less likely. The young age of the patient, no

evidence of infectious etiology found and fast progression of the disease makes a congenital abnormality a very likely possibility.

Conclusions

FS syndrome is rare in cats and FS with concurrent hepatocyte karyomegaly has not been described. Owing to the lack of exposure to known toxicants and medications, the patient's age and pure breed background, as well as clinical and histopathological findings, a congenital condition was highly suspected and genetic testing should be considered in cats with a similar presentation.

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Ethical approval The work described in this manuscript involved the use of non-experimental (owned or unowned) animals. Established internationally recognized high standards ('best practice') of veterinary clinical care for the individual patient were always followed and/or this work involved the use of cadavers. Ethical approval from a committee was therefore not specifically required for publication in *JFMS Open Reports*. Although not required, where ethical approval was still obtained it is stated in the manuscript.

Informed consent Informed consent (verbal or written) was obtained from the owner or legal custodian of all animal(s) described in this work (experimental or non-experimental animals, including cadavers) for all procedure(s) undertaken (prospective or retrospective studies). For any animals or people individually identifiable within this publication, informed consent (verbal or written) for their use in the publication was obtained from the people involved.

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