

## CASE REPORT

# Acute kidney injury manifesting as renal tubular acidosis with proximal and distal renal tubular dysfunction in a dog with acute pancreatitis

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Correction added on March 1, after first online publication: Copyright line was changed

## Abstract

**Objective:** To describe the clinical presentation and management of a critically ill dog with profound renal tubular acidosis (RTA) with proximal and distal renal tubular dysfunction.

**Case Summary:** A 3-year-old neutered female Border Terrier was presented with frequent regurgitation resulting from acute pancreatitis with severe ileus. Venous acid-base analysis and complete urinalysis confirmed the presence of normal anion gap metabolic acidosis with inappropriately alkaline urine (pH 8), consistent with distal RTA. Urinalysis, urine amino acids, and urinary fractional excretion of electrolytes revealed glycosuria (with normoglycemia), aminoaciduria, and increased fractional excretion of sodium, calcium, and phosphate consistent with generalized proximal renal tubulopathy or Fanconi syndrome. The dog responded well to supportive care and alkaline therapy and made a complete recovery.

**New or Unique Information Provided:** To the authors' knowledge, this is the first description of RTA with proximal and distal renal tubular dysfunction in the veterinary literature. Furthermore, the authors hypothesize that the transient RTA was a manifestation of acute kidney injury secondary to acute pancreatitis, the first report of this in the literature.

## KEYWORDS

canine, glomerular filtration rate, kidney injury, metabolic acidosis, tubulopathy

## 1 | INTRODUCTION

Renal tubular acidosis (RTA) refers to a group of rare kidney disorders, characterized by the presence of normal anion gap hyperchloremic metabolic acidosis in the face of normal glomerular filtration rate

(GFR). In the human literature, these disorders are classified into 4 subtypes based on the location of the tubular dysfunction. Proximal RTA (type II) occurs as a result of inability of the proximal tubules to prevent loss of bicarbonate, and distal RTA (type I) occurs as a result of inability of the distal tubule to excrete hydrogen ions. Type IV RTA occurs secondary to hypoaldosteronism and hyperkalemia in which impaired potassium excretion leads to decreased urinary ammonium excretion.<sup>1,2</sup>

**Abbreviations:** AKI, acute kidney injury; cPLI, canine-specific pancreatic lipase; DGGR, 1,2-o-dilauryl-rac-glycero-3-glutaric acid-(6'-methylresorufin); GFR, glomerular filtration rate; IRIS, International Renal Interest Society; MAP, mean arterial pressure; RER, resting energy requirement; RI, reference interval; RTA, renal tubular acidosis.

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Mixed, or type III, RTA is a poorly defined and exceptionally rare disorder only reported in human medicine. In these patients, the delineation of proximal and distal RTA is difficult to establish because there are features of both. These patients have a severe reduction in tubular reclamation of filtered bicarbonate ( $\text{HCO}_3^-$ ) alongside an inability to acidify the urine in spite of systemic acidemia. The pathophysiology reflects a genetic deficiency in the enzyme carbonic anhydrase II, resulting in a clinical syndrome termed Guibaud–Vainsel syndrome. On kidney functional studies, there is impaired reabsorption of  $\text{HCO}_3^-$ , failure to achieve maximally low urine pH, decreased  $\text{NH}_4^+$  excretion, low urine-to-blood  $\text{PCO}_2$  difference in alkaline urine, and high urinary citrate concentration, indicative of the coexistence of proximal and distal RTA.<sup>3,4</sup> To the authors' knowledge, there are no reports of an acquired form of this disease in the human literature and, furthermore, there are no reports of mixed RTA in the veterinary literature.

Rarely, proximal RTA occurs alone, but more commonly it is associated with other signs of proximal tubular dysfunction (eg, glycosuria). Several reports have described acquired, often transient, proximal tubulopathies in dogs attributed to gentamicin administration, various toxicoses, and hypoparathyroidism.<sup>5–10</sup> Acquired distal RTA has been reported in 3 dogs with immune-mediated hemolytic anemia, 1 dog each with leptospirosis and gastric-dilation-volvulus and 1 dog receiving zonisamide.<sup>11–14</sup>

Acute kidney injury (AKI) and acute pancreatitis are common comorbidities in human and veterinary medicine.<sup>15,16</sup> Although acute pancreatitis-induced AKI is well documented, tubular dysfunction secondary to acute pancreatitis is, to the authors' knowledge, not reported in either the human or veterinary literature.

The authors describe here a case of acute pancreatitis in a Border Terrier, with AKI manifesting as RTA with proximal and distal renal tubular dysfunction.

## 2 | CASE SUMMARY

A 3-year-old neutered female Border Terrier weighing 6.2 kg was presented to a referral hospital for further evaluation and treatment of acute pancreatitis with severe ileus. The dog had a 2-day history of frequent vomiting and regurgitation prior to presentation at the primary practice. There was no reported diarrhea. Clinicopathological testing performed by the referring veterinarian on day 1 revealed increased canine-specific pancreatic lipase (cPLI)<sup>a</sup> 445  $\mu\text{g/L}$  (reference interval [RI],  $\leq 200$ ) via enzyme immunoassay and increased C-reactive protein  $>100$   $\text{mg/L}$  (RI, 0–10).<sup>a</sup> An ACTH stimulation test excluded hypoadrenocorticism (basal cortisol, 450  $\text{nmol/L}$  [16.31  $\mu\text{g/dl}$ ], RI, 25–125  $\text{nmol/L}$  [0.91–4.53  $\mu\text{g/dl}$ ]; post-ACTH cortisol, 544  $\text{nmol/L}$  [19.72  $\mu\text{g/dl}$ ], RI, 125–520  $\text{nmol/L}$  [4.53–18.85  $\mu\text{g/dl}$ ]). Hematology and serum biochemistry<sup>a</sup> revealed no significant findings. The dog was hospitalized for a total of 5 days. On day 2, the dog underwent esophagoscopy and exploratory celiotomy for a suspected foreign body. Esophagoscopy revealed inflamed esophageal mucosa, and exploratory celiotomy revealed subjective enlargement of the pancreas, with the other abdominal organs considered grossly normal.

Biopsies were not taken. While hospitalized, the dog received IV crystalloid fluid therapy with Hartmann's solution<sup>b</sup> at 3  $\text{ml/kg/h}$ , alongside paracetamol<sup>c</sup> (10  $\text{mg/kg}$ , IV, q 8 h), maropitant<sup>d</sup> (1  $\text{mg/kg}$ , IV, q 24 h), and buprenorphine<sup>e</sup> (0.02  $\text{mg/kg}$ , IV, q 8 h). During this period, the dog remained anorectic with frequent regurgitation. On day 6, the dog was referred for further evaluation and treatment.

On presentation at the referral hospital, the dog was dull, laterally recumbent, and nonambulatory. Mucous membranes were pink and tacky with a prolonged capillary refill time of 3 s. There was moderate skin tenting. The dog was tachypneic, with a respiratory rate of 40/min. Cardiothoracic auscultation revealed tachycardia with a heart rate of 157/min but was otherwise within normal limits. Peripheral pulse quality was poor. The dog was estimated to be 10%–12% dehydrated. Abdominal palpation revealed no significant abnormalities and was well tolerated; however, this may have been influenced by the dog's reduced mentation. The dog regurgitated clear fluid multiple times during the consultation. The owners reported no history of diarrhea, toxin ingestion, or use of nephrotoxic drugs. Noninvasive oscillometric blood pressure measurement<sup>f</sup> was within RI (systolic 140  $\text{mm Hg}$ ; diastolic 110  $\text{mm Hg}$ ; mean arterial pressure [MAP] 127  $\text{mm Hg}$ ).

On admission to the hospital, a minimum database comprising manual PCV, total plasma protein, and blood smear examination was performed. The PCV and total plasma protein were 0.70 L/L (70%) (RI, 0.35–0.55 L/L [35%–55%]) and 78  $\text{g/L}$  (7.8  $\text{g/dl}$ ) (RI, 65–75  $\text{g/L}$  [6.5–7.5  $\text{g/dl}$ ]), respectively, consistent with hemoconcentration. Blood smear examination revealed subjective leukocytosis with no cellular atypia. CBC (in-house analyzer<sup>g</sup>) confirmed mild leukocytosis, with a total WBC count of  $23.74 \times 10^9/\text{L}$  (23,740/ $\mu\text{l}$ ) (RI,  $5\text{--}16 \times 10^9/\text{L}$  [5000–16,000/ $\mu\text{l}$ ]). Serum biochemistry (external laboratory<sup>a</sup>) revealed severely increased 1,2-o-dilauryl-rac-glycero-3-glutaric acid-(6'-methylresorufin) ester (DGGR) lipase 723.6 U/L (RI,  $\leq 200$  U/L), mildly increased alkaline phosphatase (ALP) activity (196 U/L, RI,  $\leq 130.0$  U/L), moderate hypercholesterolemia (10.13  $\text{mmol/L}$  [391  $\text{mg/dl}$ ], RI, 3.2–6.2  $\text{mmol/L}$  [123–239  $\text{mg/dl}$ ]), moderate hypoglycemia (2.79  $\text{mmol/L}$  [50.2  $\text{mg/dl}$ ], RI, 4.11–7.95  $\text{mmol/L}$  [74–143.1  $\text{mg/dl}$ ]), mild hypernatremia (153  $\text{mmol/L}$ , RI, 139–150  $\text{mmol/L}$ ), mild hyperchloremia (132  $\text{mmol/L}$ , RI, 106–127  $\text{mmol/L}$ ), and mild ionized hypercalcemia (1.64  $\text{mmol/L}$  [6.56  $\text{mg/dl}$ ], RI, 1.12–1.40  $\text{mmol/L}$  [4.48–5.60  $\text{mg/dl}$ ]). Serum proteins, phosphorus, total magnesium, and potassium were within normal limits: albumin (27  $\text{g/L}$  [2.7  $\text{g/dl}$ ], RI, 26.3–38.2  $\text{g/L}$  [2.6–3.8  $\text{g/dl}$ ]), globulin (35.0  $\text{g/L}$  [3.5  $\text{g/dl}$ ], RI, 23.4–42.2  $\text{g/L}$  [2.3–4.2  $\text{g/dl}$ ]), phosphorous (0.85  $\text{mmol/L}$  [2.6  $\text{mg/dl}$ ], RI, 0.80–1.60  $\text{mmol/L}$  [2.5–5.0  $\text{mg/dl}$ ]), magnesium (0.73  $\text{mmol/L}$  [1.77  $\text{mEq/L}$ ], RI, 0.7–1.0  $\text{mmol/L}$  [1.70–2.43  $\text{mEq/L}$ ]), and potassium (4.3  $\text{mmol/L}$ , RI, 3.6–5.6  $\text{mmol/L}$ ). There was mild azotemia: creatinine was 148  $\mu\text{mol/L}$  (1.67  $\text{mg/dl}$ ) (RI, 44–115  $\mu\text{mol/L}$  [0.5–1.3  $\text{mg/dl}$ ]) and urea was 8.4  $\text{mmol/L}$  (23.5  $\text{mg/dl}$ ) (RI, 3.1–10.1  $\text{mmol/L}$  [8.6–28.3  $\text{mg/dl}$ ]), consistent with International Renal Interest Society (IRIS) grade II AKI. A blood sample was taken directly from the jugular vein using a heparinized syringe. Whole blood was analyzed within 2 min of collection. This process was repeated each time venous blood gas analysis was performed during hospitalization. Species-specific RIs were provided by the manufacturer of the analyzer. Venous

blood gas analysis<sup>h</sup> revealed a pH of 6.893 (RI, 7.35–7.45), pCO<sub>2</sub> of 54.8 mm Hg (RI, 35.0–38.0 mm Hg), HCO<sub>3</sub><sup>-</sup> was 10.6 mmol/L (RI, 15.0–23.0 mmol/L), base excess was -13.4 mmol/L (RI, -5.0 to 0.0 mmol/L), plasma lactate was 0.40 mmol/L (RI, 0.60–2.90 mmol/L), normal anion gap (14.7 mEq/L, RI, 8–25 mEq/L), corrected chloride was 124.7 mmol/L (RI, 106–127 mmol/L), and there was a strong ion difference (SID) of 28.3 mmol/L<sup>17</sup> (RI, 34–40 mmol/L).<sup>18</sup> These findings were consistent with normal anion gap metabolic acidosis.

The dog received two 10-ml/kg boluses, each over 15 min, of Hartmann's solution<sup>b</sup> to address hypovolemia, and 2.5 ml 50% dextrose<sup>i</sup> diluted 50:50 with 0.9% saline to address hypoglycemia. The dog was sedated for diagnostic imaging using methadone<sup>j</sup> (0.2 mg/kg, IV). Thoracic radiographs were within normal limits, with no evidence of aspiration pneumonia. Abdominal ultrasonography<sup>k</sup> was performed by specialist in Veterinary Diagnostic Imaging. The right limb of the pancreas was hypoechoic, particularly close to the body. The adjacent mesentery was diffusely hyperechoic, and the duodenum had a corrugated appearance. The fundus of the stomach was atonic and contained a moderate volume of anechoic fluid. There was no evidence of a gastric outflow tract obstruction. There were multiple loops of small intestine distended with anechoic fluid with no evidence of mechanical obstruction, consistent with ileus. The kidneys were normal in size, margination, and echotexture. There was no free peritoneal fluid. Although the abnormalities of the peritoneum and duodenum could be a result of the previous exploratory celiotomy, the pancreatic changes alongside compatible clinical signs and increased cPLI and DGGR lipase were consistent with acute pancreatitis. The dog was induced with alfaxalone<sup>l</sup> (2 mg/kg, IV) and intubated with a cuffed 6.5-mm endotracheal tube. General anesthesia was maintained with isoflurane in oxygen. A jugular catheter was placed to permit regular blood sampling during hospitalization and longer term fluid therapy. An esophagostomy tube was not placed due to frequent regurgitation.

The dog's fluid deficit was subjectively corrected over 24 h. Hartmann's solution<sup>b</sup> was administered intravenously at 6 ml/kg/h with 15 mmol/L potassium chloride.<sup>m</sup> Prokinetic therapy with metoclopramide<sup>n</sup> (2 mg/kg/day, IV, as a constant rate infusion) and erythromycin<sup>o</sup> (1 mg/kg, IV, q 8 h) was used for treatment of ileus. The dog received additional supportive therapy consisting of paracetamol (10 mg/kg, IV, q 8 h), methadone<sup>j</sup> (0.2 mg/kg, IV, q 4 h), maropitant<sup>s</sup> (1 mg/kg, IV, q 24 h), and omeprazole<sup>p</sup> (1 mg/kg, IV, q 12 h). Within 4 h of commencing fluid therapy, serum creatinine decreased to 119  $\mu$ mol/L (1.35 mg/dl) (RI, 44–115  $\mu$ mol/L [0.5–1.3 mg/dl]). Eight hours following admission, the azotemia had resolved (creatinine, 97  $\mu$ mol/L [1.1 mg/dl], RI, 44–115  $\mu$ mol/L [0.5–1.3 mg/dl]), consistent with a volume-responsive AKI. On day 7, the dog's clinical status had improved, the hydration had normalized, and the dog became ambulatory and normally responsive. Blood pressure remained stable (systolic 126 mm Hg, diastolic 107 mm Hg, MAP 117 mm Hg).<sup>f</sup> Despite the improved hydration status and continued IV fluid therapy, the dog developed severe polyuria/polydipsia, constantly seeking water and drinking up to 100 ml/kg/day. Creatinine was within normal limits (60  $\mu$ mol/L [0.68 mg/dl]). However, repeat venous blood analysis revealed progressive normal anion gap metabolic acidosis:

pH was 6.81, pCO<sub>2</sub> was 55.9 mm Hg, HCO<sub>3</sub><sup>-</sup> was 10.1 mmol/L, base excess was -23.4 mmol/L, and anion gap was 17.67 mEq/L (RI, 8–25 mEq/L). The previously documented hypernatremia had also increased (164 mmol/L; RI, 139–150 mmol/L). Corrected chloride was 122 mmol/L (RI, 106–127 mmol/L), which was suggestive of a free water deficit. In spite of potassium supplementation, the dog developed moderate hypokalemia (2.7 mmol/L, RI, 3.4–4.9 mmol/L). To correct for the free water deficit, 4% glucose in 0.18% saline<sup>q</sup> was started at 2 ml/kg/h (IV).

A urine sample was concurrently acquired via cystocentesis, revealing inappropriately alkaline urine (pH 8.0) in the face of continuing acidosis. Semiquantitative urinalysis revealed glycosuria (with normal blood glucose, 5.1 mmol/L [91.9 mg/dl], RI, 3.3–6.4 mmol/L [59.5–115.3 mg/dl]), hyposthenuria (urine-specific gravity [USG] 1.005), ketonuria, and proteinuria (urinary protein creatinine ratio 5.2 [RI, <0.2]); urine bacterial culture yielded no growth. The urine sediment was inactive, with no evidence of casts or crystals. Serum proteins revealed mild hypoalbuminemia (24 g/L [2.4 g/dl], RI, 26.3–38.2 g/L [2.63–3.82 g/dl]); total plasma protein (55.6 g/L [5.56 g/dl], RI, 54.9–75.3 g/L [5.49–7.53 g/dl]) and globulin (31.6 g/L [3.16 g/dl], RI, 23.4–42.2 g/L [2.34–4.22 g/dl]) were within RIs. Urinary fractional excretion<sup>r</sup> was performed on the same sample and revealed increased excretion of sodium, calcium, phosphate, and urea and persistent glycosuria and ketonuria (Table 1). The dog was started on oral alkaline therapy with sodium bicarbonate at 1 mEq/kg/day.

On day 8, venous blood gas analysis revealed improved but persistent metabolic acidosis (pH 7.1) with improved HCO<sub>3</sub><sup>-</sup> 16.3 mmol/L. Systolic blood pressure ranged from 131 to 138 mm Hg.

By day 9, the dog's regurgitation had resolved but the dog remained anorectic; an esophagostomy tube was then placed under general anesthesia. The dog was started on a constant rate infusion of liquid diet<sup>s</sup> at one-third of resting energy requirements (RER). This was increased by one-third daily up to full RER. Repeat venous blood gas analysis revealed marked improvement in the metabolic acidosis (pH 7.321) and HCO<sub>3</sub><sup>-</sup> concentration (23.6 mmol/L). However, serum biochemistry<sup>a</sup> revealed severe hypophosphatemia (0.49 mmol/L [1.52 mg/dl], RI, 0.81–2.20 mmol/L [2.51–6.82 mg/dl]), and the dog was started on IV supplementation with sodium salt of toldimphos<sup>t</sup> (0.01 mmol/kg/h, IV). Systolic blood pressure ranged from 105 to 113 mm Hg.

On day 11, the dog's acidosis, electrolyte, and biochemical abnormalities had resolved (Table 2). Phosphorus was 1.78 mmol/L (5.5 mg/dl) (RI, 0.81–2.20 mmol/L [2.51–6.82 mg/dl]). The systolic blood pressure improved to 128–142 mm Hg. The polyuria/polydipsia had also markedly improved. The dog's alkaline therapy, fluid therapy, and phosphate supplementation were stopped. At that time, the dog became pyretic, and hematology confirmed left-shifted neutrophilia 29.0  $\times 10^9$ /L (29,000/ $\mu$ l) (RI, 3.0–12.0  $\times 10^9$ /L [3000–12,000/ $\mu$ l]), band count 2.3  $\times 10^9$ /L (2300/ $\mu$ l) (RI, <0.4  $\times 10^9$ /L [<400/ $\mu$ l]). The skin around the site of the jugular catheter was erythematous. The catheter was subsequently removed, and the pyrexia resolved.

On day 13, the dog continued to do well with no gastrointestinal signs and tolerated bolus feeding via the esophagostomy tube. Repeat

**TABLE 1** Fractional excretion of electrolytes performed on day 7

Test	Serum biochemistry	Serum reference interval	Urine supernatant biochemistry	Fractional excretion (%)	FE reference interval (%)
Sodium (mmol/L)	158	139–154	67.8	3.7%	<0.7
Potassium (mmol/L)	4.1	3.5–6.0	6.49	13.8%	<20
Total calcium (mmol/L) [mg/dl]	2.6 [10.4]	2.0–3.0 [8.0–12.0]	0.51 [2.04]	1.7%	<0.4
Phosphate (mmol/L) [mg/dl]	0.6 [1.86]	0.8–1.6 [2.48–4.95]	4.0 [12.38]	58.2%	<39.0
Urea (mmol/L) [mg/dl]	3.9 [10.92]	2.0–9.0 [0.56–25.21]	35 [98]	78.4%	14–71
Creatinine ( $\mu$ mol/L) [mg/dl]	62 [0.70]	40–106 [0.45–1.20]	0.71 [0.01]	Not assessed	Not assessed

Abbreviation: FE, fractional excretion.

**TABLE 2** Venous blood gas parameters prior to and following sodium bicarbonate therapy

Test	Day 0 <sup>a</sup>	Day 1 post-treatment	Day 2 post-treatment	Day 3 post-treatment	Day 4 post-treatment	Day 5 post-treatment	Reference interval
pH	6.81	7.101	7.32	7.29	7.36	7.41	7.35–7.45
pCO <sub>2</sub> (mm Hg) [kPa]	55.9 [7.43]	52.3 [6.96]	45.8 [6.09]	50.1 [6.66]	43.4 [5.77]	35.6 [4.73]	35–38 [4.66–5.05]
pO <sub>2</sub> (mm Hg) [kPa]	24.1 [3.21]	34.1 [4.54]	31.7 [4.22]	31.2 [4.15]	28.3 [3.76]	56.2 [7.47]	85–100 [11.3–13.3]
HCO <sub>3</sub> <sup>-</sup> (mmol/L)	10.1	16.3	23.6	24.6	24.5	22.9	15–23
Base excess (mmol/L)	-23.4	-13.4	-2.4	-1.8	-1.0	-1.6	-5.0 to 0.0
Sodium (mmol/L)	153	152	154	157	146	147	139–150
Chloride (mmol/L)	132	119	117	121	111	112	106–127
Potassium (mmol/L)	4.3	3.1	2.9	3.2	4.4	3.6	3.6–5.6
Creatinine ( $\mu$ mol/L) [mg/dl]	60 [0.68]	48 [0.54]	46 [0.52]	58 [0.66]	46 [0.52]	56 [0.63]	44–115 [0.5–1.3]

<sup>a</sup>Day 0 represents the commencement of sodium bicarbonate therapy.

urinalysis (free-catch) confirmed resolution of the glycosuria and proteinuria (urine protein creatinine ratio 0.22) with a specific gravity of 1.035 and pH 8.5. Systolic blood pressure was within RIs (131–145 mm Hg). The dog was discharged from the hospital with the esophagostomy tube in situ.

The dog was re-evaluated on day 26. The owners reported the dog to be clinically normal. The esophagostomy tube had been removed at the primary practice a week earlier. Physical examination was within normal limits. Urine (free-catch) and blood were sampled for repeat fractional excretion, which revealed an equivocal increase in excretion of

**TABLE 3** Fractional excretion of electrolytes performed on day 26

Test	Serum biochemistry	Serum reference interval	Urine supernatant biochemistry	Fractional excretion (%)	FE reference interval (%)
Sodium (mmol/L)	147	139–154	83	0.7	<0.7
Potassium (mmol/L)	4.4	3.5–6.0	77.0	21.4	<20
Total calcium (mmol/L) [mg/dl]	2.4 [9.6]	2.0–3.0 [8.0–12.0]	0.3 [1.2]	0.2	<0.4
Phosphate (mmol/L) [mg/dl]	1.3 [4.02]	0.8–1.6 [2.48–4.95]	5.0 [15.48]	4.7	<39.0
Urea (mmol/L) [mg/dl]	3.5 [9.8]	2.0–9.0 [5.6–25.21]	216 [605]	75.3	14–71
Creatinine ( $\mu$ mol/L) [mg/dl]	61 [0.80]	40–106 [0.52–1.39]	5.0 [0.07]	Not assessed	Not assessed

Abbreviation: FE, fractional excretion.

potassium and urea (Table 3) but was otherwise within the RI. Repeat examinations were not possible due to financial constraint. On telephone consultation, 3 months after referral the owners confirmed the dog was clinically well, without therapy.

### 3 | DISCUSSION

In the case presented, the inappropriately alkaline urine (pH 8.0) in the face of severe normal anion gap metabolic acidosis (pH 6.81) and low bicarbonate (10.1 mmol/L) was consistent with a distal RTA. However, the normoglycemic glycosuria, ketonuria, aminoaciduria, and increased fractional excretion of sodium, calcium, and phosphate were consistent with concurrent generalized proximal tubular dysfunction (acquired Fanconi syndrome), suggesting that this dog had RTA with abnormalities in both proximal and distal renal tubular function.

Proximal RTA occurs secondary to a deficiency in bicarbonate reabsorption in the proximal tubule; however, the ability to maximally acidify the urine is retained. Proximal RTA rarely occurs independently from other proximal tubular abnormalities. Urinary fractional excretion of electrolytes and urinary amino acids often reveal impairment of renal tubular reabsorption of other molecules, in addition to bicarbonate.<sup>1</sup>

Distal RTA is characterized by failure of the distal tubule to excrete hydrogen ions ( $H^+$ ), resulting in their combination with hydroxide ions within the tubular cell and a consequent lack of bicarbonate production. This culminates in a severe metabolic acidosis and, unlike proximal RTA, a failure to produce acidic urine (pH > 6.0).<sup>19</sup> Hyperchloremic normal-anion gap metabolic acidosis with a urine pH greater than 5.5–6 and a negative urine culture is supportive of distal RTA.<sup>1</sup>

Definitive testing to confirm the diagnosis and location of RTA involves urinary measurement of indices of acid and bicarbonate secretion. The bicarbonate loading test is used to confirm proximal RTA and is particularly useful when other proximal tubular abnormalities are absent. An increase in urinary bicarbonate concentration following bicarbonate infusion confirms impaired reabsorption and proximal RTA. Conversely, definitive diagnosis of distal RTA is made with an ammonium chloride loading test, the principle being that the adminis-

tration of oral ammonium chloride should acidify urine in a normally functioning kidney in an attempt to buffer blood pH, whereas with impaired urinary  $H^+$  and  $NH_4^+$  secretion in distal RTA, urinary pH will not decrease.<sup>2</sup> The furosemide/fludrocortisone test represents an alternative provocation of distal acidification.<sup>2</sup> The bicarbonate challenge test was not performed in our case due to the presence of other proximal tubular abnormalities identified on fractional excretion supportive of generalized proximal tubular dysfunction. Tests to confirm distal RTA were not performed due to the risks of both tests on an unstable patient and due to the fact that the dog met the main diagnostic criteria previously described for people, which have been reportedly used for dogs.<sup>1,2</sup>

Measurement of the fractional excretion of bicarbonate and urine anion gap represent additional tests to localize the tubular dysfunction and confirm proximal and distal RTA, respectively. Unfortunately, fractional excretion of bicarbonate was not offered at the external laboratory used to perform the urinary fractional excretion test, and fractional excretion of chloride was not performed in this case.

Differential diagnoses for the inappropriately alkaline urine in the face of severe acidosis include intravascular volume depletion and urinary tract infection by urea-splitting organisms.<sup>2</sup> The latter was excluded based on the negative urine culture and inactive urine sediment, whereas the increased fractional excretion of sodium would not be consistent with hypovolemia because activation of the renin–angiotensin–aldosterone system would be expected to increase sodium reabsorption. Severe diarrhea can lead to a normal anion gap metabolic acidosis through loss of bicarbonate but was not present in this dog.

The hypernatremia alongside increased fractional excretion of sodium was an interesting finding in this case as it is not a typical finding in RTA. Sodium diuresis due to impaired sodium glucose transporter function at the proximal convoluted tubule is not uncommon in cases of proximal RTA. However, due to the importance of sodium, the nephron is able to reclaim sodium additionally in the thick ascending loop of Henle. This was demonstrated in a study in which healthy cats were administered the sodium–glucose cotransporter type-2 inhibitor, dapagliflozin. The test population demonstrated no increase in fractional extraction of sodium compared to the control population. The



authors inferred this was due to an increase in absorption of sodium via the sodium–potassium transporter in the thick ascending loop of Henle.<sup>20</sup> Indeed, human patients with distal RTA tend to experience urinary potassium wasting and hypokalemia prior to therapy because sodium reabsorption in the collecting tubules occurs more in exchange with potassium, as the net distal hydrogen ion secretion is diminished.<sup>2</sup>

The increased fractional excretion of sodium discovered in this case would suggest that these compensatory mechanisms were overwhelmed. The hyponatremia therefore initially appears contradictory in the face of sodium diuresis. Taken alongside the normal corrected chloride, the hyponatremia can likely be attributed to a free water deficit, suggesting there was loss of electrolyte-poor water in spite of wasting electrolytes in terms of the fractional excretion. This is consistent with nephrogenic diabetes insipidus, in which the distal and collecting tubules are unable to respond to antidiuretic hormone (ADH), and provides further evidence for a distal tubular lesion in this case.

Uremic acidosis would represent an alternative differential for the acid–base status of the dog. At referral, the dog demonstrated signs consistent with hypovolemia and creatinine concentration consistent with IRIS grade II AKI. However, RTA is distinguished from uremic acidosis by normal or only slightly reduced GFR and normal anion gap acidosis. The GFR, by plasma iothexol clearance or plasma exogenous creatinine clearance,<sup>21</sup> could not be measured on an emergency basis in our dog. In uremic acidosis, the underlying mechanisms of acid secretion are maintained; therefore, H<sup>+</sup> excretion per functioning nephron is in fact increased, resulting in a normal response to an acid load that cannot be excreted because of too few nephrons rather than the intrinsic ability of the nephron itself. Uremic acidosis was therefore excluded on the basis of a rapid reduction in creatinine with fluid therapy, normotensive blood pressure during hospitalization, lack of renal sonographic changes, and the absence of an increased anion gap.

In the veterinary literature, the etiology of proximal RTA in dogs has been well documented as idiopathic hereditary (Fanconi syndrome in Basenji Hounds and other breeds)<sup>22</sup> or acquired secondary to various diseases (multiple myeloma, hypoparathyroidism, copper-associated hepatopathy),<sup>9,10</sup> toxins (heavy metals, ethylene glycol, Chinese chicken jerky treats),<sup>8,23</sup> infections (leptospirosis, pyelonephritis),<sup>5</sup> or drugs (gentamicin, streptozotocin, tetracyclines).<sup>6,24,25</sup> In the case presented here, the dog had no history of toxin ingestion, exposure to nephrotoxic drugs or chemicals, and had never been fed jerky treats. Although urine culture can be negative in dogs and people with acute pyelonephritis,<sup>26,27</sup> the negative urine culture, sonographically normal kidney architecture, and resolved azotemia without the use of antimicrobials make pyelonephritis less likely in this case.

Similar to proximal RTA, distal RTA can be a transient or permanent disorder and can represent a congenital abnormality or an acquired disease secondary to a primary insult of renal or nonrenal origin. The etiology of distal RTA is less well documented in veterinary medicine but has been reported in dogs and cats secondary to immune-mediated hemolytic anemia,<sup>11</sup> pyelonephritis,<sup>28,29</sup> gastric-dilatation-volvulus,<sup>12</sup> leptospirosis,<sup>13</sup> and zonisamide therapy.<sup>14</sup>

To the authors' knowledge, this report documents the first case of RTA with proximal and distal tubular dysfunction in the veterinary

literature. An association between renal tubular dysfunction and pancreatic cancer and chronic pancreatitis is reported in human medicine.<sup>21</sup> However, there are no reports specifically on acute pancreatitis and tubular dysfunction in either the human or veterinary literature. Acute pancreatitis is a common condition with a wide spectrum of disease, ranging from mild self-limiting to fulminant illness that results in systemic inflammatory response syndrome.<sup>30</sup> Clinical history, ultrasound findings, and increased cPLI and DGGR lipase met the diagnostic criteria for acute pancreatitis in this case. Acute pancreatitis and AKI are well-documented comorbidities in both human and veterinary medicine, with an estimated prevalence in dogs of up to 26.2%.<sup>16</sup> Acute pancreatitis can lead to AKI via hypovolemia, cytokine-induced ischemia, inflammation, and oxidative stress.<sup>15,31</sup> Although capability of H<sup>+</sup> excretion is often preserved in AKI, 1 veterinary study demonstrated that acute renal ischemia in dogs could be associated with a defect in distal tubular acidification, most likely of secretory type.<sup>32</sup> Therefore, it is the authors' hypothesis that the associated hypovolemia and proinflammatory state generated an acute and reversible kidney injury affecting the proximal and distal tubules and resulting in the development of severe, transient RTA.

The primary alternative differential for the findings presented in this case is leptospirosis. Certainly, the tubular injury, polyuria/polydipsia, increased ALP activity, pancreatitis, and AKI could be consistent with this disease. The dog's recovery without the use of antimicrobials does not rule out leptospirosis because spontaneous recovery with supportive care alone is reported in human patients. On the other hand, the dog had no evidence of thrombocytopenia, anemia (seen in approximately 50% of cases), hyperbilirubinemia, or renal sonographic findings consistent with the disease.<sup>33</sup> The increased ALP could be explained by cholestasis secondary to pancreatitis, especially given the hypercholesterolemia. Nevertheless, the authors accept that a transient renal tubular injury secondary to colonization of renal tubules by *Leptospire*s was possible in this case. The authors hope it raises awareness to fellow clinicians that confirmatory testing for leptospirosis by paired microscopic agglutination test titers (MAT) or polymerase chain reaction (PCR) on blood and urine is indicated in dogs presenting with evidence of RTA.

The mainstay of therapy for all forms of RTA is bicarbonate therapy. In veterinary medicine, the recommended initial dose is 1.0–1.5 mEq/kg BW per day of sodium bicarbonate in divided doses, but higher doses (up to 4 mEq/kg BW/day) may be required to maintain normal pH.<sup>1</sup> Our dog responded well to the initial dose of 1 mEq/kg/day, improving within 24 h with sustained resolution of the acidosis within 4 days of administration. This was an interesting finding and hypothetically may help to localize the source of the dog's acidosis. The bicarbonate dose required to correct metabolic acidosis tends to be higher for proximal RTA compared to distal RTA. As with all other solutes, there is a maximum rate for bicarbonate reabsorption in the proximal tubule known as the transport maximum ( $T_m$ ). In proximal RTA, the  $T_m$  is reduced (12–20 mEq/L compared to 24–26 mEq/L in normal dogs<sup>34</sup>), resulting in urinary loss of bicarbonate. However, once the plasma bicarbonate level equates to the new  $T_m$ , a new steady state is achieved in which the amount of bicarbonate filtered

by the glomerulus equals the resorptive capacity of the tubule.<sup>19</sup> Consequently, as bicarbonate is supplemented during treatment, the plasma bicarbonate again rises above the  $T_m$ , allowing bicarbonate loss in urine. Dogs with proximal RTA can require over 10 mEq/kg/day of bicarbonate to keep up with renal losses and correct pH disturbances. On the other hand, acidosis associated with distal RTA is usually corrected with doses of 1–3 mEq/kg/day.<sup>1</sup> Based upon this dog's complete response to 1 mEq/kg/day sodium bicarbonate, it is the authors' hypothesis that although the dog experienced transient proximal tubular dysfunction, the source of its marked acidosis is more attributed to impaired  $H^+$  excretion from distal tubular dysfunction than impaired bicarbonate resorption.

In conclusion, this is the first case report of an AKI manifesting as RTA with proximal and distal renal tubular dysfunction in a dog with acute pancreatitis. It was hypothesized that the hypovolemia and proinflammatory state of the acute pancreatitis generated an acute and reversible IRIS grade II AKI, resulting in proximal and distal tubulopathies that manifested as severe, transient RTA. Although RTA is a rare disorder, pancreatitis and associated AKI are not uncommon in veterinary medicine. This case report raises awareness of this condition in dogs at risk of AKI and documents the intensive monitoring and therapeutics required to support these critically ill patients with complex acid–base and electrolyte disorders.

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## ENDNOTES

- <sup>a</sup> IDEXX Laboratories, Wetherby, Yorkshire.
- <sup>b</sup> Hartmann's solution for injection BP, Aquapharm 11, Animalcare Ltd, York, North Yorkshire.
- <sup>c</sup> Perfalgan 10 mg/ml solution for infusion, Bristol-Myers Squibb Pharmaceuticals Limited, Uxbridge, Middlesex.
- <sup>d</sup> Prevomax 10 mg/ml solution for injection for dogs and cats, Dechra Veterinary Products, Hadnall, Shropshire.
- <sup>e</sup> Vetergesic 0.3 mg/ml solution for injection for dogs and cats, Ceva Animal Health Ltd, Amersham, Bucks.
- <sup>f</sup> Cardell model 9401, Midmark Corporation, Versailles.
- <sup>g</sup> IDEXX ProCyt Dx Haematology Analyser, IDEXX Laboratories, Wetherby, Yorkshire.
- <sup>h</sup> epoc Portable Blood Gas Electrolyte and Critical Care Analyser, Woodley Equipment Company Ltd, Bolton, Lancashire.
- <sup>i</sup> Glucose intravenous infusion BP 50% w/v, Hameln Pharmaceuticals Limited, Gloucester Business Park, Gloucester.
- <sup>j</sup> Comfortan 10 mg/ml solution for injection for dogs and cats, Dechra Veterinary Products, Hadnall, Shropshire.
- <sup>k</sup> Samsung RS80, micro-convex transducer CF4-9 MHz, 1 focal zone, DR65 FR32Hz, Samsung Electronics (UK) Ltd, Chertsey, Surrey.
- <sup>l</sup> Alfaxalan Multidose 10 mg/ml, Jurox (UK) Ltd, Crawley, West Sussex.
- <sup>m</sup> Potassium chloride concentrate 20%, Hameln Pharmaceuticals Limited, Gloucester Business Park, Gloucester.
- <sup>n</sup> Metoclopramide 5 mg/ml injection, Hameln Pharmaceuticals Limited, Gloucester Business Park, Gloucester.
- <sup>o</sup> Erythromycin lactobionate, 1 g powder for solution for infusion, Advanz Pharma, London, UK.
- <sup>p</sup> Omeprazole, 40 mg powder for solution for infusion, Bowmed Ibisqus Limited, Chirk, Wrexham.

<sup>q</sup> Aquapharm 18 solution for infusion, Animalcare Ltd, York, North Yorkshire.

<sup>r</sup> Veterinary Pathology Group, Hitchin, Hertfordshire.

<sup>s</sup> Royal Canin Gastrointestinal Low-Fat diet, Crown Pet Foods, Castle Cary, Somerset, UK.

<sup>t</sup> Foston 20% w/v solution for injection, MSD Animal Health, Walton, Milton Keynes.

## CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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