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URATE NEPHROLITHIASIS IN A NORTHERN ELEPHANT SEAL (*MIROUNGA ANGUSTIROSTRIS*) AND A CALIFORNIA SEA LION (*ZALOPHUS CALIFORNIANUS*)

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Abstract: Nephrolithiasis has rarely been reported in marine mammals. During 2004 and 2005, two cases of nephrolithiasis were diagnosed during routine necropsy examination, one in a northern elephant seal (*Mirounga angustirostris*) and one in a California sea lion (*Zalophus californianus*). Nephroliths were found throughout both kidneys during necropsy examination, varying in size from 1–10 mm in diameter in the northern elephant seal and from 1–15 mm in diameter in the California sea lion. Necropsy and histopathology revealed nephroliths in association with renal pelvic dilation and pyelonephritis in both animals. In addition, hydronephrosis was noted in the sea lion. Nephroliths were composed of uric acid and ammonium urate in the northern elephant seal and of ammonium urate in the California sea lion. The underlying disease leading to nephrolith formation was not determined; however, it is hypothesized that unknown metabolic derangements due to morphologic or physiologic differences may have played a role. This is the first report of urate nephrolithiasis in the California sea lion and northern elephant seal.

Key words: California sea lion, *Mirounga angustirostris*, northern elephant seal, nephrolithiasis, urate nephrolith, *Zalophus californianus*.

INTRODUCTION

Uroliths are abnormal mineral salt concretions or stones found in the urinary tract.[40] Relatively uncommon in marine and domestic mammals, they are most frequently reported in dogs and cats. Uroliths may be found incidentally or may be associated with pain, hematuria, or clinical manifestations secondary to urinary tract obstruction or infection.[2,27] Struvite and calcium oxalate are the most frequently diagnosed uroliths in dogs and cats. Purine uroliths, composed of uric acid and its salts or xanthine, are the third most common uroliths in dogs and cats, accounting for 6% of feline and 8% of canine urolith cases.[28] Documented cases of uroliths in marine mammals include urate nephrolithiasis in a harbor seal (*Phoca vitulina*); urate nephrolithiasis in a river otter (*Lontra canadensis*); struvite penile urethrolithiasis in a pygmy sperm whale (*Kogia breviceps*); two cases of calcium carbonate nephrolithiasis in West Indian manatee (*Trichechus manatus*); and urate and struvite vaginal calculi in bottlenose dolphins (*Tursiops truncatus*).[9,15,23,24,33,38,42]

The term urate refers to uroliths composed of uric acid, ammonium urate, and other uric acid salts (e.g., sodium acid urate, sodium calcium urate, and ammonium calcium urate). In cats, urate uroliths are composed of uric acid and the monobasic ammonium salt of uric acid (ammonium acid urate), whereas in dogs they are usually composed of ammonium acid urate.[6,29]

This report describes two cases of urate nephrolithiasis in pinnipeds. To the best of our knowledge, these are the first reports of nephrolithiasis in a California sea lion (*Zalophus californianus*) and a northern elephant seal (*Mirounga angustirostris*).

CASE REPORT 1: NORTHERN ELEPHANT SEAL

A male weanling northern elephant seal that stranded in San Luis Obispo County, California (USA), was admitted to The Marine Mammal Center in Sausalito, California (TMMC), in May 2004. The seal weighed 42.5 kg and was classified as moderately underweight based on morphometric measurements, weight, and general appearance. Age was determined based on size, stage of tooth eruption, and the time of year (northern elephant seals are born in January). Two small puncture wounds with no discharge were noted on the left cheek and left flank. A blood sample was collected

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Table 1. Serum biochemistry parameters for the northern elephant seal.

Parameter[a]	Day 1	Day 19	Day 54	Reference range[b]
Sodium (mEq/L)	142.0	147.0	126.0	143–154
Potassium (mEq/L)	4.0	5.3	4.0	4.7–6.1
Chloride (mEq/L)	100.0	97.0	88.0	98–107
BUN (mg/dl)	22.0	42.0	144.0	33–76
Creatinine (mg/dl)	0.4	0.5	0.6	0.2–0.8
Glucose (mg/dl)	119.0	144.0	49.0	128–189
Calcium (mg/dl)	9.9	10.7	8.9	10.2–12.8
Phosphorous (mg/dl)	5.6	9.8	6.9	6.6–9.9
Uric acid	1.1	3.7	1.4	
Total protein (g/dl)	5.4	7.4	7.9	6.6–9.9
Albumin (g/dl)	2.6	3.4	2.8	3.2–3.9
Globulin (g/dl)	2.8	4.0	5.1	3.1–6.1
Total bilirubin (mg/dl)	0.9	0.4	1.0	0.1–0.6
GGT (mg/dl)	338.0	125.0	137.0	22–136
LDH (U/L)	418.0	471.0	493.0	223–542
AST (U/L)	167.0	53.0	71.0	39–117
ALT (U/L)	81.0	62.0	62.0	18–65
ALKP (U/L)	163.0	173.0	89.0	108–454
Iron (U/L)	152.0	149.0	45.0	
Cholesterol (μg/dl)	196.0	161.0	90.0	34–249
Triglycerides (mg/dl)	86.0	94.0	153.0	100–347

[a] BUN, blood urea nitrogen; GGT, gamma glutamyl transferase; LDH, lactate dehydrogenase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALKP, alkaline phosphatase.

[b] Reference ranges from Bossart et al. (2001).[3]

for complete blood count (Vet ABC hematology analyzer, Heska Corporation, Fort Collins, Colorado 80525, USA), manual differential count, and serum chemistry profile (AU5200, Olympus America, Inc., New York, New York 11747, USA). To collect samples for these tests, the epidural venous sinus was accessed using a 21-gauge, 1.5-inch needle, and the sample was divided into Vacutainer® (BD, 1 Becton Drive, Hanklin Lakes, New Jersey 07417 USA) tubes.[3]

Table 2. Complete blood count and manual differential count for the northern elephant seal.

Parameter[a]	Day 1	Day 19	Day 54	Reference range[b]
WBC ($\times 10^3 mm^3$)	12.9	33	72.2	10.6–35
RBC ($\times 10^3 mm^3$)	3.55	3.77	3.67	2.6–3.3
HGB (g/dl)	23.7	23.7	22.2	16.2–24.2
MCV (fl)	170	167	160	170–185
MCH (pg)	66.7	62.8	60.6	63–74
PLT ($\times 10^3 mm^3$)	282	743	373	355–652
Segs (%)	53	72	68	
Bands (%)	1	0	23	
Eos (%)	2	3	0	
Basos (%)	0	0	0	
Lymphs (%)	40	18	2	
Monos (%)	4	7	5	

[a] WBC, white blood cells; RBC, red blood cells; HGB, hemoglobin; MCV, mean cell volume; MCH, mean cell hemoglobin; PLT, platelets; Segs, segmental neutrophils; Eos, eosinophils; Basos, basophils; Lymphs, lymphocytes; Monos, monocytes.

[b] Reference ranges from Bossart et al. (2001).[3]

Management

Analysis of serum biochemistry compared to the reference range for this species (Table 1) revealed a mild hypoproteinemia and an increase in gamma glutamyl transferase (GGT) activity that was consistent with malnutrition.[3,11] A nutritional plan with supplemental fluids was initiated and consisted of feedings of fish mash (half-thawed herring and half water by volume, liquidized), with an additional 20 ml of salmon oil administered via oro-gastric tube t.i.d. In addition, the northern elephant seal was encouraged to eat whole fish once daily. A second blood sample was drawn on day 19, and all parameters were within the reference range (Tables 1, 2). The seal started to eat thawed whole herring voluntarily, but stopped abruptly on day 45. Tube feeding was reinstated to provide caloric requirements and to maintain hydration. Nine days later, 54 days post–initial presentation, the seal's gums started to bleed, and it became dehydrated. Moreover, the seal exhibited a dull and lethargic demeanor. Ulcerated

necrotic areas appeared within 24 hr on the mandibular and maxillary mucosa. A third blood sample was taken for hematology and serum biochemistry analysis and revealed a leukocytosis with a left shift; an elevated blood urea nitrogen (BUN); hypernatremia; hyperglobulinemia; and mild hypoalbuminemia compared to the previous results (Tables 1, 2).[3]

Leptospirosis or *Otostrongylus circumlitus* infection with dehydration were considered to be the differential diagnoses based on the clinical appearance of the seal, the blood results, and the history of diseases in northern elephant seals admitted to TMMC.[4,10,36] Treatment for these infections began on day 55 and consisted of administration of 1,000 mg (p.o.) amoxicillin b.i.d. (STADA Pharmaceuticals, Inc., Cranbury, New Jersey 08512, USA) and 50 mg (p.o.) ketoprofen once daily (TEVA Pharmaceuticals USA, Sellersville, Pennsylvania 18960, USA), administered via an oro-gastric tube with food. In addition, 2,000 ml/day of lactated Ringer's solution was given subcutaneously (Hospira, Inc., Lake Forrest, Illinois 60045, USA). Four milligrams of ivermectin (MSD-AgVet Merck, Division of Merck and Co., Inc., Rahway, New Jersey 07065, USA) was administered subcutaneously on day 56. On day 58, the seal exhibited hematemesis, and feeding via oro-gastric tube was discontinued for 24 hr. The seal's clinical condition progressively deteriorated, and euthanasia was performed by injecting 10 ml of 39% pentobarbital sodium and 5% phenytoin sodium (Beuthanasia-D Special®, Schering-Plough Animal Health Corp., Union, New Jersey 07083, USA) into the epidural venous sinus.

Necropsy

Necropsy was performed within an hour of death. Gross necropsy revealed evidence of gingival bleeding, epistaxis, and moderate gastrointestinal hemorrhage. The left kidney was grossly enlarged compared to the right. Multiple nephroliths surrounded by purulent exudate were observed in the markedly dilated pelvices of the left kidney. The nephroliths varied in size from 1 by 2 mm to 7 by 10 mm. They were irregularly shaped and diffusely green-brown. Smaller nephroliths were present in the pelvices of the right kidney. Uroliths and granular material were present in the urinary bladder and urethra, but no obstruction of the ureters or urethra was found. There were a large number of *Anisakis* spp. in the stomach. Representative tissue samples from several organs were fixed in 10% neutral-buffered formalin, routinely processed for paraffin embedding, sectioned at 5 μm, and stained with hematoxylin and eosin and Brown and Brennen's stain. Microbiology swabs were taken from the left kidney and the left lung and were submitted along with liver and kidney tissue for bacterial culture.[41] Nephroliths were collected from both kidneys and sent for analysis by chemical reaction to Idexx Laboratories (Idexx Veterinary Services, West Sacramento, California 95605, USA).

Histopathology

Histologic findings included bilateral, multifocal, suppurative, and necrotizing pyelonephritis with nephrolithiasis. Rare clusters of gram-negative bacteria were noted within the pelvices. The lesions were more severe in the left compared to the right kidney. Suppurative lymphadenitis was noted in the renal lymph node. Mild multifocal neutrophilic hepatitis was also noted. In addition, superficial mucosal necrosis, ulceration, and vascular mineralization compatible with uremic gastritis were present in the stomach. No histologic lesions suggestive of a porto-systemic shunt were found.

Microbiology

Salmonella enterica subsp. *enterica* (formerly *Salmonella typhimurium*) was isolated from liver and kidney tissues and from the swab taken from the kidney.

Nephrolith analysis

The nephroliths were irregular in shape with a smooth, green-brown surface. Nephroliths were composed of ammonium urate and uric acid.

CASE REPORT 2: CALIFORNIA SEA LION

An adult female California sea lion that stranded in Monterey County, California (USA), in April 2005 was admitted to TMMC for evaluation. The sea lion weighed 37 kg. Age and sex were determined using morphometric measurements, weight, and observations of genitalia and teeth.[8] Weight loss and body condition were evaluated as moderate by general appearance. Dehydration was estimated by the degree of emaciation, the sunken appearance of the eyes, and the mucoid consistency of the tears. A blood sample was taken for serum biochemistry parameters, manual differential count, and a complete blood count, performed as described above. To collect blood samples, the caudal gluteal vein was accessed using a 21-gauge, 1.5-inch needle, and the samples were divided into Vacutainer® tubes.

Management

Serum biochemistry and complete blood count revealed a leukopenia with a left shift; azotemia;

Table 3. Serum biochemistry parameters for the California sea lion.

Parameter[a]	Value	Reference range[b]
Total bilirubin (mg/dl)	1.39	0.1–0.4
BUN (mg/dl)	127.9	14–38
Total protein (mg/dl)	9.52	9–11
Phosphorous (mg/dl)	12.19	1.8–7.8
Creatinine (mg/dl)	1.89	0–1.4
Cholesterol (μg/dl)	112.7	102–269
Calcium (mg/dl)	10.45	8.5–11.2
AST (U/L)	108	13–166
Albumin (g/dl)	2.45	2.9–4.0
ALKP (U/L)	66	9–175
ALT (U/L)	43	9–175
Glucose (mg/dl)	85.6	62–135
Sodium (mEq/L)	175.7	143–162
Potassium (mEq/L)	5.17	4.1–5.7
Chloride (mEq/L)	130	101–115
Globulin (g/dl)	7.07	4.1–7.4

[a] BUN, blood urea nitrogen; AST, aspartate aminotransferase; ALKP, alkaline phosphatase; ALT, alanine aminotransferase.
[b] Reference ranges from Bossart et al. (2001).[3]

Table 4. Complete blood count and manual differential count for the California sea lion.

Parameter[a]	Value	Reference range[b]
WBC ($\times 10^3$/mm^3)	4.7	9.4–22.8
RBC ($\times 10^3$/mm^3)	3.2	2.9–4.8
HGB (g/dl)	10	11.2–16.7
HCT (%)	29.4	28.0–56.0
PLT ($\times 10^3$/mm^3)	412	192–708
MCV (fl)	92	89–123
MCH (pg)	31.2	32.0–41.0
MCHC (g/dl)	34	30.0–39.0
Segs (%)	59	
Bands (%)	15	
Lymphs (%)	14	
Monos (%)	12	

[a] WBC, white blood cells; RBC, red blood cells; HGB, hemoglobin; HCT, hematocrit; PLT, platelets; MCV, mean cell volume; MCH, mean cell hemoglobin; MCHC, mean cell hemoglobin concentration; Segs, segmented neutrophils; Lymphs, lymphocytes; Monos, monocytes.
[b] Reference ranges from Bossart et al. (2001).[3]

mild hyperbilirubinemia; hypernatremia; hyperkalemia; hyperchloremia; and hyperphosphatemia (Tables 3, 4).[3] A presumptive diagnosis of leptospirosis was made based on serum biochemistry alterations, clinical signs, age, and body condition of the sea lion.[12,13,36] Treatment was initiated with 750,000 U of Penicillin G Benzathine and 750,000 U of Penicillin G Procaine (Dual Pen®, G.C. Hanford Mfg. Co., Syracuse, New York 13201, USA) administered every other day by i.m. injection and 2,000 ml/day lactated Ringer's solution (Hospira, Inc., Lake Forrest, Illinois 60045, USA) administered subcutaneously. The sea lion voluntarily started to drink fresh water and became polydipsic by day 4. Thawed whole herring was offered, but the sea lion remained anorectic and developed dark, tarry, watery feces. On day 5 there was an acute deterioration in the sea lion's clinical condition, and the sea lion was euthanized with 200 mg tiletamine-zolazepam combination i.m. (Telazol®, Fort Dodge Animal Health, Fort Dodge, Iowa 50501, USA) to induce deep sedation followed by the administration of 10 ml of 39% pentobarbital sodium and 5% phenytoin sodium i.v. into the subclavian vein.

Necropsy

Necropsy was performed within 1 hr of death. Gross abnormalities included bilateral renal enlargement and diffuse pallor of the liver. There were numerous multifocal 2–3 mm diameter tan firm nodules scattered throughout the lung parenchyma, and the sea lion had a severe *Parafilaroides* sp. infestation. Palpation of the kidneys revealed crepitus associated with the presence of several nephroliths within the renal pelvices. Renal cortices were diffusely pale tan, and the pelvices had moderate to severe hydronephrosis. Nephroliths ranged in size from 1 to 15 mm in diameter, were light tan to gray in color, and were found in the pelvis of each renule. No uroliths were observed in the ureters, bladder, or urethra. Representative tissue samples from several organs were fixed in 10% neutral-buffered formalin and processed as described above. Representative nephroliths were collected from both kidneys and sent for crystallographic analysis to the University of California, Davis (Urinary Stone Analysis Department, School of Veterinary Medicine, Department of Medicine and Epidemiology, Davis, California 95616-8737, USA).

Histopathology

Histologic findings included bilateral hydronephrosis, with the left kidney more severely affected than the right kidney. Chronic lymphoplasmacytic pyelonephritis, interstitial fibrosis, and glomerulosclerosis were all present to varying degrees in both kidneys. Fragments of nephroliths were visualized within the renal pelvices. Severe chronic plasmacytic ureteritis and urethritis and a mild lymphocytic and neutrophilic cystitis were noted. Throughout the lungs, there were multifocal granulomas along with lymphoplasmacytic interstitial pneumonia and bronchiolitis associated with adult and lar-

val metastrongyles nematodes consistent in appearance with *Parafilaroides decorus*. There was no evidence of secondary infection in the sections of the liver observed.

Nephrolith analysis

All nephrolith surfaces were smooth to rough in texture, with a chalky appearance, and were light tan to gray. The nephroliths were cross-sectioned, revealing a surface layer of crystals, an outer fine layer of medium, tan concentric rings, and a small chalky central core, all composed entirely of uric acid.

DISCUSSION

We report two cases of urate nephrolithiasis in pinnipeds: uric acid nephrolithiasis in a California sea lion and compound nephrolithiasis (ammonium urate and uric acid) in a northern elephant seal. Nephroliths composed of urate and uric acid have been identified in pinnipeds in a harbor seal from a small marine aquarium.[38] Uric acid stones are classified, based on crystalline composition, as anhydrous uric acid, uric acid dehydrate, sodium acid urate monohydrate, or ammonium acid urate.[14] Ammonium urate and uric acid are the most common forms of urate uroliths found in cats, whereas ammonium urate accounts for 90% of urate uroliths in dogs.[28]

Uric acid is the end product of purine metabolism in humans, great apes, New World monkeys, and Dalmatian dogs.[16,18,21,35] In other mammals, uric acid is further broken down into allantoin by the enzyme uricase. Allantoin is 10–100 times more soluble than uric acid. Uric acid may be derived by endogenous or exogenous routes. The endogenous production of uric acid from tissue catabolism and de novo synthesis is relatively constant, whereas the exogenous pool varies substantially with diet. Serum concentrations of uric acid are tightly regulated in mammals, controlled by renal excretion and by transformation into allantoin.[16,18,21,35] However, serum uric acid concentrations are extremely variable in marine mammals.[3,32]

Uric acid urolith formation requires urine supersaturation with uric acid. Three factors contribute to the formation of these uroliths: acidic urine, hyperuricuria, and decreased urinary volume.[2,26] One or more of these conditions may coexist in a specific patient and may contribute to urolithiasis. Increased dietary intake of purines and purine precursors (e.g., high-protein diets) may lead to hyperuricemia and consequent hyperuricosuria, facilitating urate urolith formation.[21,30] The normal pinnipedia diet is fish-based and is therefore naturally very high in purines.[26,27] Urate urolith formation is common in dogs and cats with hepatic portosystemic shunts.[22] Those patients have a concurrent hyperuricuria, hyperuricemia, hyperammonemia, and hyperammonuria. Urate urolith formation may also occur in patients without hepatic porto-systemic shunts, in which case it is likely secondary to a metabolic derangement.[17,21] Dalmatian dogs are prone to developing urate uroliths as a result of the reduced rate at which they convert uric acid to allantoin, compared to other canine breeds. Daily urinary excretion of uric acid is 10 to 60 times higher in Dalmatians than in other dog breeds.[1,18,30]

Nephroliths can be an incidental finding or may be associated with urinary tract infection or obstruction. Struvite as well as other unidentified nephroliths have previously been found incidentally in harbor seal pups.[38,39] Urolith formation can occur secondary to infection by urease-producing organisms. These bacteria split urea, leading to an increase in urinary ammonia concentration and pH, which favors precipitation of struvite crystals. The resulting hyperammonuria could increase the risk of urate uroliths.[31] Hyperammonuria, however, creates an alkaline urine pH, which increases urate solubility, thus explaining the lack of reports of infection-induced urate stones in dogs and cats. In carnivores, there remains an association between nephrolithiasis and secondary infection. In one study, approximately 60% of dogs with nephroliths had urinary tract infections, whereas in another study, only 8% of cats with ureteral uroliths had concurrent infection.[19,20] The identification of non–urease producing bacteria within the urinary tract represents opportunistic infections able to take advantage of urolith-induced alterations to this environment.[20] *Salmonella* spp. are commonly isolated from pinnipeds and have been previously isolated from a dog with nephroliths.[5,20,37,41] Histopathologic findings from the northern elephant seal were compatible with a systemic infection affecting the liver and kidneys, and *Salmonella enterica* subsp. *enterica* was isolated from both organs. Despite the absence of a pronounced increase in creatinine concentration 5 days prior to death, clinical and necropsy findings were consistent with uremic crisis. Oral ulcers and gingival bleeding may occur in uremic patients but are also common in this species in association with sepsis and disseminated intravascular coagulopathy (DIC).[10]

It is likely that the northern elephant seal reported here suffered from acute renal failure and pyelonephritis in association with nephrolithiasis that progressed to sepsis and uremia, thereby triggering DIC.[31]

Nephroliths can cause intermittent or persistent urinary tract obstruction. Obstruction of the renal pelvis of one kidney may not result in clinical signs if the urinary tract is sterile and the contralateral kidney has normal function.[34] Hydronephrosis and hydroureter are common findings in cats with ureteral uroliths.[19] In this case, hydronephrosis was found at necropsy in both animals. Pyelectasia also can be found secondary to pyelonephritis, but the degree of dilation in these animals was severe, and along with the absence of hydroureter and ureteral uroliths, this finding indicates intrarenal obstruction as the underlying etiology.[25]

Treatment of urate uroliths in dogs and cats consists of correction of the underlying problem (such as surgical correction of a hepatic porto-systemic shunt), surgical removal of nephroliths and uroliths, and prevention of recurrences with allopurinol and dietary management.[2] Surgical urolith removal from reniculate kidneys would be difficult, as nephroliths tend to lodge in the many small pelvices. Long-term medical management and dietary modification to prevent further nephrolith formation make treatment of this condition an unrealistic option in marine mammal rehabilitation.[11]

The underlying disease leading to formation of urate nephroliths in the northern elephant seal and California sea lion reported here was not identified. As in most cats and dogs with no evidence of portosystemic shunts, it is hypothesized that a metabolic derangement was present. Although there are only a very small number of documented cases of uroliths in marine mammals, the single previous urolith report in an adult pinniped from which chemical composition of uroliths was determined was also urate.[38] This finding may indicate that pinnipeds preferentially form urate uroliths, and further investigation in this area is warranted.

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