

Bilateral Uric Acid Nephrolithiasis and Ureteral Hypertrophy in a Free-ranging River Otter (*Lontra canadensis*)

Robert A. Grove,^{1,4} Rob Bildfell,² Charles J. Henny,¹ and Donald R. Buhler³ ¹USGS-Forest and Range Ecosystem Science Center, 3200 SW Jefferson Way, Corvallis, Oregon 97331, USA; ²OSU Veterinary Diagnostic Laboratory, College of Veterinary Medicine, Oregon State University, P.O. Box 429, Corvallis, Oregon 97339-0429, USA; ³Department of Environmental and Molecular Toxicology, Oregon State University, ALS 1007, Corvallis, Oregon 97331, USA; ⁴Corresponding author (email:robert_grove@usgs.gov)

ABSTRACT: We report the first case of uric acid nephrolithiasis in a free-ranging river otter (*Lontra canadensis*). A 7 yr old male river otter collected from the Skagit River of western Washington (USA) had bilateral nephrolithiasis and severely enlarged ureters (one of 305 examined [0.33%]). The uroliths were 97% uric acid and 3% protein. Microscopic changes in the kidney were confined to expansion of renal calyces, minor loss of medullary tissue, and multifocal atrophy of the cortical tubules. No inflammation was observed in either kidney or the ureters. The ureters were enlarged due to marked hypertrophy of smooth muscle plus dilation of the lumen. Fusion of the major calyces into a single ureteral lumen was several cm distal to that of two adult male otters used as histopathologic control specimens. This case report is part of a large contaminant study of river otters collected from Oregon and Washington. It is important to understand diseases and lesions of the otter as part of our overall evaluation of this population.

Key words: *Lontra canadensis*, river otter, ureter hypertrophy, uric acid nephrolithiasis, urolithiasis.

Uroliths (urinary calculi) are concretions that can form at any level of the urinary tract and are usually composed of inorganic salts, organic acids, or other compound such as cystine, xanthine, or silica. The most common uroliths in mammals are composed of calcium as an oxalate or phosphate, magnesium as ammonium or hydrogen phosphate, purines, and cystine (Cotran et al., 1994; Osborne et al., 1995). Uric acid uroliths make up less than 1% of total uroliths analyzed in dogs and cats (Osborne et al., 1995), and from 4–40% of uroliths in humans (Shekarri and Stoller, 2002). Urolithiasis has been reported in a few species of the family Mustelidae (Chaddock, 1947; Sompolinsky, 1950; Keymer et al., 1981; Thomlinson et al., 1982).

In particular, some otters such as the Asian small-clawed otter (*Aonyx cinerea*) have a high incidence of calcium oxalate mono and dihydrate urolithiasis (Keymer et al., 1981; Karesh, 1983; Nelson, 1983; Calle and Robinson, 1985; Petrini, 1999) in captivity. Urolithiasis has not previously been reported in river otters (*Lontra canadensis*). Little is known about normal renal function of river otters or adaptations in renal physiology necessary for their largely aquatic life (Hoover and Tyler, 1986). The anatomy of the river otter kidney is described in detail in Baitchman et al. (2000). In short, the kidney of otters is reniculated (Hoover and Tyler, 1986; Baitchman et al., 2000). This renal architecture is absent in other mustelids but present in sea otters (*Enhydra lutris*), pinnipeds, cetaceans, and a few other mammals (Baitchman et al., 2000). The significance of reniculated kidneys in otters but not in other mustelids is unknown.

An adult male river otter (RAG-245) was trapped as part of a larger study at the mouth of the Sauk River on the Skagit River, near Rockport, Washington (USA, 48°28'54.44"N, 121°36'15.18"W) in January 1997. The otter was frozen at –20 C until necropsy was performed in July 1997 at the Veterinary Diagnostic Laboratory, College of Veterinary Medicine, Oregon State University (Corvallis, Oregon, USA). The otter's age was estimated to be 7 yr by microscopic analysis of cementum annuli from an upper canine tooth (Matson's Laboratory LLC, Milltown, Montana, USA) as described by Fancy (1980) and Matson (1981). During necropsy, body condition was evaluated and morphometric information recorded. Major organs

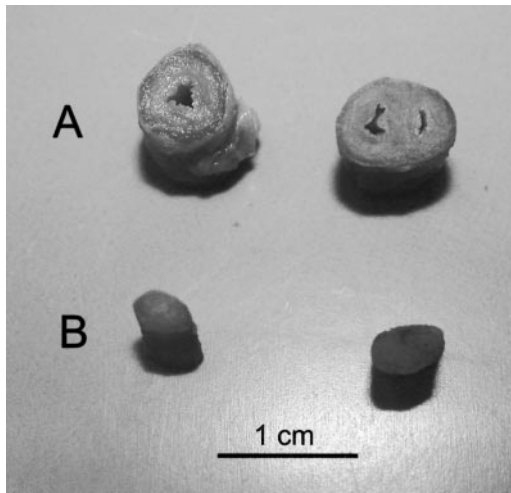


FIGURE 1. Cross sections of a ureter from the affected adult male river otter RAG-245 (top row **A**) and a ureter from a control adult male (bottom row **B**). Specimens on the left side of each row were collected 3 cm proximal to bladder. Specimens on the right side of each row were collected 3 cm distal to renal hilus.

were weighed and measured and abnormalities noted. Sections of abnormal tissues were preserved in 10% buffered formalin and histologic slides were prepared and stained with hematoxylin and eosin.

The otter had bilaterally enlarged ureters (Fig. 1). We used urogenital tracts of similar age adult male otters as controls for gross and microscopic comparisons. A normal ureter is approximately 4.5 mm in diameter (Fig. 1), while the diameter of the ureters of the affected otter were 8 mm. The proximal $\frac{2}{3}$ of each abnormal ureter was composed of three distinct lumina measuring approximately 1 mm in diameter. These lumina gradually converged, with the distal $\frac{1}{3}$ of the ureter having a single lumen 3 mm in diameter. This point of union was several cm distal to that of the two luminal passages seen in the control otter. The muscular walls of the abnormal ureters at this point were approximately 2.5 mm thick.

Calculi were present in all minor calyces of the kidneys (Fig. 2). Calculi were removed, rinsed in distilled water, and air dried. A total of 4.9 g (3.2% of kidney



FIGURE 2. Left kidney of adult male river otter RAG-245, showing several stones (arrows) within the minor calyces.

weight) of calculi were removed from the two kidneys. Mean calculus diameter was 6.02 mm ($n=30$, $SD=0.75$ mm), with diameters ranging from 4.52 to 7.76 mm. A sample of the calculi was sent to Louis C. Herring and Company, Analytical and Consulting Chemists (Orlando, Florida, USA), for integrated crystallographic analysis. The calculi were analyzed as described by Lloyd and Oldroyd (1983). Uric acid stones are classified based on crystalline composition, of which the anhydrous form is the most stable. The calculi were found to be composed of compact masses of monoclinic crystals of anhydrous uric acid, indicating homogeneous nucleation. Protein matrices were demonstrated. The calculi were composed of 97% uric acid and 3% protein.

Histologic examination of the abnormal kidneys revealed expansion of the renal calyces with concurrent loss of medullary tissue. Two of the four calyces observed contained lamellated masses of basophilic, non-refractile, and finely filamentous material consistent with urates. Medullary tubules contained unidentified green-brown crystalline debris. Multifocal atrophy of cortical tubules was found with concomitant increase in the proportion of interstitial collagen in these areas. Ureteral changes were characterized by hyperplasia of the urothelial layer and a remarkable hypertrophy of the smooth muscle component. No cellular infiltrates suggestive of an inflammatory component were found in the ureters or kidneys.

Uric acid (2,6,8-trioxypurine) is the end product of purine metabolism which is derived by both endogenous and exogenous routes via a series of enzymatic reactions involving xanthine oxidase (Shekarriz and Stoller, 2002). Endogenous uric acid production results from de novo purine synthesis and tissue catabolism under normal circumstances. However, the exogenous pool varies widely with diet, with diets rich in animal protein (such as the river otter's diet) contributing significantly to the uric acid pool. Hoover and Tyler (1986) reported river otter mean fasting uric acid serum levels of 2.01 (± 0.66) mg/dl; Ben-David et al. (2001) reported similar findings. The primary mode of uric acid clearance is through urinary excretion, accounting for about two-thirds of its elimination. Almost all serum uric acid is in the ionized form (monosodium urate) with $\sim 5\%$ of the urate bound with serum protein at physiologic pH. Uric acid is completely filtered at the renal glomerulus. Two factors contribute to uric acid solubility: uric acid concentration and solution pH (Shekarriz and Stoller, 2002). Uric acid is a weak acid with two dissociation constants (pKa's at pH of 5.5 and 10.3) of which the second pKa is of no physiologic significance. Supersaturation of urine with uric acid occurs when urine pH is less than 5.5, causing uric acid precipitation and subsequent urolithiasis in a few cases. Hoover and Tyler (1986) reported mean river otter urine pH at 6.22 with a pH range of 5.0–9.0. Therefore, the factors that usually contribute to uric acid calculi formation are acidic urine, hyperuricosuria, and dehydration with low urinary volume or stasis.

Bilateral ureteral hypertrophy is often a consequence of obstruction at the level of the urinary bladder or urethra, but no lesions were detected in these portions of the urinary tract. Decreased ureteral function can lead to intra-renal urine stasis, which may promote nephrolith formation. It is postulated that the abnormal ureters in this otter may have been an important predisposing factor to the development of

nephrolithiasis. Comparison with more otters is required to determine if the unusual fusion of major calyces seen in this case represented a congenital anomaly.

Approximately 50% of human uric acid nephrolithiasis cases are idiopathic. However, certain predisposing factors specific to this condition have been identified. These include defects in protein metabolism, as is seen in Dalmations or in dogs with portosystemic shunts (Osborne et al., 1995). Otters are carnivorous and thus must metabolize large amounts of purine compounds, yet little is known about uric acid metabolism and clearance in this species. Reference serum biochemical values for uric acid suggest river otters produce uric acid in quantities similar to other mammalian species (Swenson, 1993; Kaneko et al., 1997). There was no opportunity for antemortem assessment of protein metabolism in RAG-245 but the animal was in excellent body condition with normal muscle mass.

Urease-splitting bacteria within the affected portion of the urinary tract may also promote uric acid urolith formation (Maxie, 1993). Bacterial cultures were not attempted, but the lack of any inflammation in the renal or ureteral tissue makes such an infection unlikely.

We are currently evaluating the river otter as a potential sentinel species for monitoring persistent environmental contaminants (e.g., polychlorinated biphenyls, dioxins, furans) because of its position as a top predator in most aquatic food chains. It is important to document and understand diseases and lesions associated with this species which might affect interpretations of findings concerning contaminant exposure and accumulation. Also, the large number of river otters examined during our study provided a unique opportunity to discover some of the rarer lesions not normally found in studies of smaller groups of animals.

We gratefully acknowledge V. R. Bentley for his assistance during necropsies, and K. Fisher for her assistance in the

preparation of histology slides. This study was funded through both the U.S. Geological Survey and U.S. Fish and Wildlife Service.

LITERATURE CITED

- BAITCHMAN, E. J., AND G. V. KOLLIAS. 2000. Clinical anatomy of the North American river otter (*Lontra canadensis*). *Journal of Zoo and Wildlife Medicine* 31: 473–483.
- BEN-DAVID, M., L. K. DUFFY, AND T. BOWYER. 2001. Biomarker responses in river otters experimentally exposed to oil contamination. *Journal of Wildlife Diseases* 37: 489–508.
- CALLE, P. P., AND P. T. ROBINSON. 1985. Glucosuria associated with renal calculi in Asian small-clawed otters. *Journal of the American Veterinary Medical Association* 11: 1149–1153.
- CHADDOCK, T. T. 1947. Veterinary problems of the fur ranch. *Veterinary Medicine* 42: 409.
- COTRAN, R. S., V. KUMAR, AND S. L. ROBBINS. 1994. The kidney. In *Pathologic basis of disease*, 5th Edition, F. J. Schoen (ed.). W. B. Saunders Company, Philadelphia, Pennsylvania, pp. 927–989.
- FANCY, S. G. 1980. Preparation of mammalian teeth for age determination by cementum layers: A review. *Wildlife Society Bulletin* 8: 242–248.
- HOOVER, J. P., AND R. D. TYLER. 1986. Renal function and fractional clearances of American river otters (*Lutra canadensis*). *Journal of Wildlife Diseases* 22: 547–556.
- KANEKO, J. J., J. W. HARVEY, AND M. L. BRUSS. 1997. Clinical biochemistry of domestic animals, 5th Edition. J. J. Kaneko, J. W. Harvey and M. L. Bruss (eds). Academic Press, San Diego, California, pp. 890–903.
- KARESH, W. B. 1983. Urolithiasis in Asian small-clawed otters (*Amblyonyx cinerea*). In *Annual proceedings of the American Association of Zoo Veterinarians*, M. E. Fowler (ed.). Tampa, Florida, pp. 42–44.
- KEYMER, I. F., G. LEWIS, AND P. L. DON. 1981. Urolithiasis in otters (Family Mustelidae—Subfamily lutrinae) and other species. In *Erkrankungen der Zootiere, Verhandlungs-breicht dex XXIII Internationalen Symposiums Uber die Erkrankungen der Zootiere*. R. Ippen (ed.). Halle/Saale, Deutsche Demokratische Republik, pp. 391–401.
- LLOYD, D. T., AND N. O. OLDROYD. 1983. Analysis of urinary calculi. In *International perspectives in urology*, J. A. Libertino (ed.), Vol. 6. Stones, clinical management of urolithiasis. R. A. Roth and B. Finlayson (eds.). Williams and Wilkins Company, Baltimore, Maryland, pp. 8–20.
- MATSON, G. M. 1981. Workbook of cementum analysis. Matson's Laboratory, Milltown, Montana, 30 pp.
- MAXIE, M. G. 1993. The urinary system. In *Pathology of domestic animals*, 4th Edition, K. V. F. Jubb, P. C. Kennedy and N. C. Palmer (eds.). Academic Press, San Diego, California, pp. 447–522.
- NELSON, G. H. 1983. Urinary calculi in two otters (*Amblyocix sernaria*). *Journal of Zoo Animal Medicine* 14: 72–73.
- OSBORNE, C. A., J. P. LULICH, J. W. BARTGES, R. THUMCHAI, L. A. KOEHLER, K. A. BIRD, AND L. J. FELICE. 1995. Canine and feline urolithiasis: Relationship of etiopathogenesis to treatment and prevention. In *Canine and feline nephrology and urology*, C. A. Osborne and D. R. Finco (eds.). Williams & Wilkins, Philadelphia, Pennsylvania, pp. 798–888.
- PETRINI, K. R., J. P. LULICH, L. TRESCHER, AND R. F. NACHREINER. 1999. Evaluation of urinary and serum metabolites in Asian small-clawed otters (*Aonyx cinerea*) with calcium oxalate urolithiasis. *Journal of Zoo and Wildlife Medicine* 30: 54–63.
- SHEKARRIZ, B., AND M. L. STOLLER. 2002. Uric acid nephrolithiasis: Current concepts and controversies. *The Journal of Urology* 168: 1307–1314.
- SOMPOLINSKY, D. 1950. Urolithiasis in mink. *Cornell Veterinarian* 40: 367–377.
- SWENSON, M. J. 1993. Physiological properties and cellular and chemical constituents of blood. In *Duke's physiology of domestic animals*, 11th Edition, M. J. Swenson and W. O. Reece (eds.). Comstock Publishing Associates, Cornell University Press, Ithaca, New York, pp. 22–48.
- TOMLINSON, M. J., V. PERMAN, AND R. L. WESTLAKE. 1982. Urate nephrolithiasis in ranch mink. *Journal of the American Veterinary Medical Association* 180: 622–626.

Received for publication 10 March 2003.