Journal of Zoo and Wildlife Medicine 35(3): 397–399, 2004

DIAGNOSIS AND TREATMENT OF PRESUMPTIVE PYELONEPHRITIS IN AN ASIAN ELEPHANT (*ELEPHAS MAXIMUS*)

Carlos R. Sanchez, D.V.M., M.Sc., Suzan Murray, D.V.M., Dipl. A.C.Z.M., Richard J. Montali, D.V.M., Dipl. A.C.V.P., Dipl. A.C.Z.M., and Lucy H. Spelman, D.V.M., Dipl. A.C.Z.M.

Abstract: A 37-yr-old female Asian elephant (*Elephas maximus*) presented with anorexia, restlessness, and dark-colored urine. Urinalyses showed hematuria, leukocyturia, isosthenuria, proteinuria, granular casts, and no calcium oxalate crystals. Bloodwork revealed azotemia. Urine culture revealed a pure growth of *Streptococcus zooepidemicus* resistant to sulfamethoxazole–trimethoprim but susceptible to cephalosporins. A presumptive diagnosis of pyelonephritis was made based on bloodwork, urinalysis, and urine culture. The animal was treated with intravenous ceftiofur, and intravenous and per rectum fluids were given for hydration. The elephant's attitude and appetite returned to normal, the abnormal blood parameters resolved, and urinary calcium oxalate crystals reappeared after treatment, supporting presumptive diagnosis. Follow-up ultrasonography revealed an abnormal outline of both kidneys with parenchymal hyperechogenicity and multiple uterine leiomyomas.

Key words: Hematuria, Asian elephant, *Elephas maximus*, pyelonephritis, calcium oxalate crystals.

BRIEF COMMUNICATION

A 4,280-kg, 37-yr-old female Asian elephant (*Elephas maximus*), housed at the Smithsonian National Zoological Park (SNZP) in a group of three animals, was managed in a free contact setting and was accustomed to regular blood sampling from the auricular veins. The elephant had chronic stiffness and muscle atrophy associated with a left forelimb fracture sustained when it was 10-yr-old. It had been treated with long-term, low-dose ibuprofen (Ibuprofen tablets 600 mg, Schein Pharmaceutical, Inc., Florham Park, New Jersey 07932, USA; 1.2 mg/kg, p.o., s.i.d.). In March 2001, the elephant became partially anorexic and restless with repeated stretching of its hind limbs and began to pass dark, rust-colored urine. The animal was mildly dehydrated based on dry mucous membranes, thick saliva, and tachycardia (60 beats/min, normal = 25–30 beats/min).[10] The hematocrit was elevated at 0.435 L/L ($\bar{x}$ = 0.372 ± 0.058 L/L),[7] but total protein was within reference intervals. No pyrexia was noted. The hemogram revealed a mild leukopenia (6.70 cells × 10^9/L; $\bar{x}$ = 13.36 ± 3.46 cells × 10^9/L)[7] and possible monocytopenia (0.98 cells × 10^9/L; $\bar{x}$ = 3.84 ± 2.92 cells × 10^9/L).[7] Serum chemistry values were unremarkable. A clean free-catch urine sample revealed hematuria with moderate leukocyturia, although no intracellular bacteria were seen. Urine sediment cytology revealed numerous red blood cells (RBCs), prominent cellular casts containing neutrophilic and epithelial cell remnants, and a notable lack of the calcium oxalate crystals normally found in elephant urine.[2] Urine was submitted for bacterial culture.

Ibuprofen therapy was discontinued in case the renal disease was drug induced. Pending urine culture results, the elephant was started on sulfamethoxazole–trimethoprim (sulfamethoxazole–trimethoprim tablets 800 mg/160 mg, Teva Pharmaceuticals Inc., Sellersville, Philadelphia, Pennsylvania 18960, USA; 15 mg/kg, p.o., s.i.d.). Clinical signs were unchanged the next morning. The elephant consumed hay but refused concentrates and showed no interest in extra oral fluids. Repeat laboratory tests showed elevated creatinine (221 mmol/L; $\bar{x}$ = 141 ± 27 mmol/L)[7] and continued hematuria. The blood urea nitrogen (BUN) was within reference intervals but moderately elevated for this particular elephant (5.355 mmol/L; $\bar{x}$ = 4.641 ± 1.428 mmol/L).[7] The hemogram was unchanged.

On day 4, the elephant became completely anorexic, depressed, and weak and spent much of its time leaning against a wall. Moderate dehydration was noted with worsening azotemia (BUN = 7.14 mmol/L, creatinine = 300.56 mmol/L). Urinalysis showed hematuria with mild leukocyturia (1–3 white blood cells [WBC]/high-power field), isosthenuria (sp. gr. = 1.009; normal = 1.016–1.023),[1] proteinuria (3+), and numerous granular casts containing WBCs, RBCs, Gram(+) cocci, and tubular cells. The absence of calcium oxalate crystals persisted. A pure culture of *Streptococcus zooepidemicus* was isolated from the initial free-catch urine sample, which was resistant to sulfamethoxazole–trimethoprim but susceptible to cephalosporins.

Antibiotic therapy was changed to ceftiofur (Naxcel, Pharmacia & Upjohn Company, Kalamazoo, Michigan 49001, USA; 6 g, i.v., t.i.d.). In addition, i.v. fluid therapy was initiated using two 14-

From the Smithsonian National Zoological Park, 3001 Connecticut Avenue NW, Washington, D.C. 20008-2598, USA. Correspondence should be directed to Dr. Sanchez.

ga, 50-mm over-the-needle catheters (Terumo Surflash I.V. Catheter, Terumo Medical Corporation, Somerset, New Jersey 08873, USA) placed in the left auricular veins sutured and glued to the skin. The maintenance fluid rate for this elephant, based on 40 ml/kg/day as used in horses, was 120 L/day. Only 54 L of lactated Ringer's solution (Abbot Laboratories, North Chicago, Illinois 60064, USA) was administered on the first day, but the elephant was more responsive to keepers that evening although it continued to show no interest in food or oral fluids and urinated only a limited amount of red-colored urine. The next day, the elephant was profoundly lethargic and somnolent. Fluid therapy was increased to 40 L i.v. t.i.d. in three 2.5-hr sessions, separated by a 2-hr rest period. In addition, 20 L of water was delivered via rectal enema (using a soft rubber hose and tap water) three times a day. Approximately half the water introduced rectally was not retained. By that evening, the elephant was more responsive and began to urinate more frequently. The following day, the fluid therapy regimen was modified to allow the elephant more time to eat and drink, by reducing daily i.v. fluid sessions to two (40 L each). Rectal fluid treatments were decreased in volume to 10 L but increased in frequency to five times a day. With this regimen, the elephant received a total fluid volume of 130 L. The same regimen was followed for the next 2 days until the elephant began drinking water regularly and would not stand still for i.v. fluid therapy. Rectal fluids were tolerated for an additional 3 days.

On day 5 of ceftiofur therapy, i.m. administration was attempted, but the elephant resisted the second injection, and i.v. therapy was resumed for a total of 7 days and then switched to cephalexin (Cephalexin capsules 500 mg, Novopharm USA Inc., Schaumburg, Illinois 60173, USA; 50 g, p.o., b.i.d.) for 8 wk. Repeat urinalysis on day 10 revealed mild hematuria and moderate leukocyturia characterized mainly by mononuclear cells. Calcium oxalate crystals were again present. The elephant continued to regain strength and appetite, and the hemogram showed marked leukocytosis (32.2 cells $\times$ 10^9/L) with monocytosis (19.9 cells $\times$ 10^9/L). The serum chemistry values were within reference intervals. The leukocytosis resolved 3 wk after initiation of treatment with oral cephalexin.

After 8 wk of oral cephalexin, the elephant remained clinically normal, and the hemogram and serum chemistries were within reference intervals, although urinalysis revealed RBC and WBC. A repeat urine culture from a free-catch sample isolated *Escherichia coli* with no growth of the original *Streptococcus*. Antibiotic therapy was switched to enrofloxacin (Baytril Film Coated tablets 68 mg, Bayer Corporation, Shawnee Mission, Kansas 66201, USA; 10 g, p.o., b.i.d., for 4 wk). During the subsequent 3 mo, routine urinalysis continued to reveal variable numbers of RBCs and WBCs.

In July 2001, 3 mo after initial presentation, a transrectal ultrasonographic evaluation of the kidneys was performed under standing sedation (Butorphanol tartrate 10 mg, i.v., Torbugesic, Fort Dodge Animal Health, Iowa 50501, USA) in an attempt to elucidate the origin of the intermittent urinary RBC. Both kidneys had abnormal outlines, prominent renal vasculature, and moderate diffuse hyperechogenicity of their parenchyma. In addition, multiple leiomyomas of the uterine tissue were observed. At 17 mo after treatment, the elephant showed no sign of clinical disease, but monthly urinalyses continue to show low numbers of RBCs with occasional WBCs. Calcium oxalate crystals are routinely present in all urine samples.

The clinical signs noted in this elephant are consistent with those observed in cattle and horses with acute pyelonephritis. In domestic large animals, these signs include dysuria manifested by hematuria or pyuria, fever, anorexia, weight loss, and depression.[4,6] Diagnostic evaluation of pyelonephritis in large animals is based on physical examination, bloodwork, urinalysis, ultrasonic imaging, endoscopy, and biopsy.[5,9] In this elephant, the combination of history, clinical signs, physical examination, blood work, and urinalysis led to a presumptive diagnosis of pyelonephritis. Profound lethargy and depression associated with azotemia, low urine specific gravity, and urinary casts with neutrophils were indicative. Although a kidney biopsy technique for a juvenile African elephant exists,[8] this procedure was considered too invasive given the previous diagnostic information and positive response to treatment. The increased ultrasonographic echogenicity of the kidneys correlated with findings of tubular degeneration and replacement fibrosis in horses with previous pyelonephritis.[3,9] The clinical course of the disease and this elephant's response to treatment closely mirrored those in domestic animals with pyelonephritis.[4,6]

The i.v. route ensured delivery of antibiotics to the renal tissue in a dehydrated and anorectic animal. Fluid therapy, both i.v. and per rectum, was instrumental in reversing dehydration, promoting diuresis, and enhancing delivery of antibiotics to the renal tissue. Intravenous fluid therapy was well tolerated initially by the elephant. Rectal therapy was easily accomplished and should be considered as an alternate or adjunctive route for hydration or

to correct electrolyte imbalance or acid–base abnormalities in ill elephants. Sequential blood analyses and urinalyses provided a valuable indication of clinical status and response to treatment. The leukopenia noted on initial examination was interpreted as a normal response to an overwhelming local infection. The WBC count returned to normal, coincident with the elephant's recovery after 4 wk of therapy. Pyuria and gross hematuria resolved, urinary specific gravity returned to normal, the casts disappeared, and oxalate crystals were present.

The pattern of varying crystalluria in elephants is not well understood. Calcium oxalate and carbonate crystals have been described in the urine of healthy Asian elephants.[2,12] At SNZP, calcium oxalate crystals have been noted in all female Asian elephants, including the one involved in this case. However, during the initial stages of illness, these crystals were not noted. Once azotemia resolved, crystals were once again apparent. A similar lack of crystals had been reported previously in an elephant with renal disease.[12] The presence of such crystals may serve to function not only as an indicator of renal health but perhaps a measure of response to treatment.

An etiology for pyelonephritis was not determined in this elephant. Ibuprofen administration has been considered a potential cause of the development of pyelonephritis, however. Several elephants at SNZP have undergone long-term treatment with low-dose ibuprofen with no observed side effects. In this case, casts with Gram(+) cocci were evident in the urine sample. The culture isolation of a single species of *Streptococcus* rather than a multiple species of bacteria suggests that infection was due to the isolated *Streptococcus* and is consistent with acute renal damage associated with urinary tract infection rather than drug-induced nephrotoxicity.[11] An ascending bacterial infection from the lower urinary tract or reproductive system may have initiated pyelonephritis. After normal renal function was regained, treatment with ibuprofen was restarted, and to date, no signs of renal disease have reoccurred. The significance of variable low numbers of RBC on routine urinalysis remains unclear but may be due to the presence of the leiomyomas in the reproductive tract.

LITERATURE CITED

1. Benedict, F. G. 1936. The Physiology of the Elephant. Publication no. 474. Carnegie Institution of Washington., Washington, D.C.

2. Benedict, F. G., and R. C. Lee. 1938. Further observations on the physiology of the elephant. J. Mammal. 19: 175–194.

3. Divers, T. J. 1984. Diagnosis and management of urinary tract infections in the horse. Proc. Symp. Trimethoprim/Sulfadiazine Pp. 31–37.

4. Divers, T. J. 2002. Urinary tract infections. *In:* Smith, B. P. (ed.). Large Animal Internal Medicine, 3rd ed. Mosby Inc., St. Louis, Missouri. Pp. 834–836.

5. Divers, T. J., and A. E. Yeager. 1995. The value of ultrasonographic examination in the diagnosis and management of renal diseases in horses. Equine Vet. Educ. 7: 334–341.

6. Hodgson, D. R. 1987. Cystitis and pyelonephritis. *In:* Robinson, N. E. (ed.). Current Therapy in Equine Medicine, 2nd ed. W. B. Saunders Co., Philadelphia, Pennsylvania. Pp. 708–712.

7. International Species Information System. 1999. Physiological Data Reference Values for *Elephas maximus*, Females, >30 years. International Species Information System, Apple Valley, Minnesota.

8. Jensen, J. 1986. Paralumbar kidney biopsy in a juvenile African elephant (*Loxodonta africana*). Proc. Am. Assoc. Zoo Vet. P. 17.

9. Kisthardt, K. K., J. Schumacher, S. T. Finn-Bodner, S. Carson-Dunkerley, and M. A. Williams. 1999. Severe renal hemorrhage caused by pyelonephritis in 7 horses: clinical and ultrasonographic evaluation. Can. Vet. J. 40: 571–576.

10. Kock, R. A., P. Morkel, and M. D. Kock. 1993. Current immobilization procedures used in elephants. *In:* Fowler, M. E. (ed.). Zoo & Wild Animal Medicine, Current Therapy 3. W. B. Saunders Co., Philadelphia, Pennsylvania. Pp. 436–441.

11. MacLeay, J. M., and C. W. Kohn. 1998. Results of quantitative cultures of urine by free catch and catheterization from healthy adult horses. J. Vet. Intern. Med. 12: 76–78.

12. Morris, P. J., J. P. Held, and J. M. Jensen. 1987. Clinical pathologic features of chronic renal failure in an African elephant (*Loxodonta africana*). Proc. Intl. Conf. Zool. Avian Med. Pp. 468–472.

Received for publication 5 November 2002