Reptile Renal Visceral Gout

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Introduction

Gout is a disease caused by deposition of urate crystals in tissues. These crystals of uric acid can accumulate in various areas of the body, forming tophi and causing the different forms of gout; visceral, articular, and periarticular. It was first described by Hippocrates 2500 years ago as a disease of the joints and was named according to which joint was affected: Podagra (big toe), Cheigagra (hand) and Gonagra (knee). However, most of what we know today about gout has only been discovered during the last few decades. In some vertabrates, including humans, nonhuman primates, the Dalmation dog, birds and some reptiles, the end product of purine degradation from dietary protein ingestion is uric acid (4). This creates the potential for high levels of uric acid in the urine and blood. Mammals, specifically humans and primates, experience gout because of an inherited purine degradation defect. While fairly common and extensively researched in humans and primates, not much research is available in veterinary medicine. Although common in reptiles, gout is not often seen in the mammalian species of veterinary medicine, although Dalmatians are predisposed to urate bladder stones due to a defect resulting in inefficient transport of uric acid in both the liver and renal proximal tubules (1). The frequency of gout in reptiles has been reported to be 16% (11). Although all three forms have been noted in many reptile species, this case report will focus on visceral renal gout found in a rat snake.

History and Presentation

Toby, an approximately 12 year old male rat snake, presented to MSU CVM Community Veterinary Service on January 11, 2017 for a mass noted on the caudal third of his body and a

history of decreased defecation, anorexia and weight loss. He lives in a 10 gallon aquarium that is heated with overhead lamps and a thermopad underneath. The floor is covered in wood shavings and he is given a constant supply of fresh water. He is offered thawed mice once per week. His last noted defecation and meal of a medium mouse (13-18g) was three months prior to presentation, although decreased defecation had been noted previously. His anorexia had led to a subsequent weight loss of 140g since the mass was first seen. The mass was first noted three months prior to presentation and had dramatically increased in size by the time of examination. A warm water bath was given along with administration of warm water and mineral oil into his cloaca in an attempt to pass the waste material, but was unsuccessful.

Upon presentation, Toby was bright, alert, and responsive. He weighed 450g (1.0 lb) and had a visible vertebral ridge due to prominent vertebrae and overall thin body condition. There is an approximately 5 cm in diameter round mass within the caudal third of coelom. Impacted feces were palpated cranial to mass. All other aspects of physical exam were within normal limits.

Pathophysiology

Reptile kidneys, while metanephric, vary vastly from mammalian kidneys. Physiologically, the most notable difference relevant to this report is how uric acid is cleared from the body. As protein is metabolized, the nucleic acids are degraded into nucleotides and even further into purine and pyrimidine bases. Unused purines are then degraded, forming uric acid, which is excreted from the body. In mammals, uric acid is excreted in the form of urea via filtration in the kidneys. In reptiles, uric acid is cleared via active secretion by the proximal tubules in the kidneys (4,11).

Persistent hyperuricemia and renal dysfunction result in gout (11). Uric acid crystallizes and forms insoluble precipitates that are deposited in the tissue and cause a granulomatous inflammatory reaction, forming small white nodules called tophi (5). In renal visceral gout, tophi form on mesothelial surfaces and within the parenchyma of the kidneys (6). Other common sites of deposition in visceral gout in reptiles include the pericardial sac, liver, spleen, lungs, and subcutaneous tissue. In the early stage of disease, uric acid crystals will gradually accumulate within the tubular epithelial cells around the center of origin. In later stages, the crystals will break through the basement membrane, forming tophi and eventually form large yellow-white confluent masses (9).

Gout can be classified as primary or secondary. In primary gout, hyperuricemia is a result of an overproduction of uric acid. In mammals, primary gout is responsible for almost all cases and is caused by an inherited defect in purine metabolism. In secondary gout, the hyperuricemia is a result of an acquired disease that interferes with the normal production and excretion of uric acid. In reptiles, gout is caused by either excessive protein metabolism or catabolism with uric acid production overcoming the uric acid excretion (6). The most commonly seen conditions resulting in secondary gout include starvation, renal disease, severe and prolonged dehydration and excessive dietary purines (2,4). Drugs may also cause gout by affecting kidney function. The most commonly associated drugs are diuretics, however nephrotoxic antibiotics such as aminoglycosides and the sulfonamides can cause tubular nephrosis and lead to hyperuricemia. Hypovitaminosis A has also been associated with the development of gout (5).

Diagnostic Approach/Considerations

A definitive diagnosis of visceral gout is made by demonstrating urate crystals within the tophi of diseased tissues. However, gout is most commonly diagnosed based on history and clinical signs in reptile patients. Environmental history questions are especially important since most reptile gout cases are contributed to environmental imbalances. Diet, availability of water, ambient temperature and humidity are all predisposing factors that can play a role in development of the disease.

Although diagnosing renal dysfunction or failure would help support the diagnosis of gout, it is often challenging in reptilian patients. Blood urea nitrogen and creatinine are usually unreliable in evaluating kidney function. Alkaline phosphatase and alanine aminotransferase are both enzymes that are released by renal cell damage, but they enter into the urine and not the blood. Elevated levels of uric acid may indicate renal failure, but this value is not specific or sensitive. Hyperuricemia doesn't occur until two thirds or more of functional renal mass is lost (2). Uric acid levels may also increase 5-10 times the preprandial value after a high-protein meal and are highly influenced by hydration (6). Elevated phosphorous concentrations are the most reliable way to assess renal function, although high phosphorous diets, ovulation and hypervitaminosis D3 also commonly result in hyperphosphotemia.

Radiographs may reveal renal or cystic calculi if they have been complexed with calcium, however they will go unnoticed if they are solely composed of monosodium urate (4). Visceral renal gout may also be evaluated and diagnosed on necropsy. Grossly, reptile kidneys are reddish brown with convoluted surfaces. They are separated into lobules with elongated, rounded segments (12). In cases of gout, tophi can be seen as small yellow/white nodules or masses of confluent nodules on the surface or within the tissues of the kidneys.

Once a sample of suspected tophi has been taken (fine needle aspirate, biopsy, necropsy sample, etc.), it must be evaluated for urate crystals. Tophi consist of radially arranged uric acid crystals surrounded by inflammatory cells including macrophages, some giant cells, and varying numbers of heterophilic granulocytes and lymphocytes. In cystic kidneys, accumulations of uric acid crystals may be seen in the tubular lumen. In nondilated tubules, several clusters of uric acid may be identified close together and may block the lumen (11).

Treatment and Management

Advanced stages of gout in reptiles are not considered treatable and are associated with a poor prognosis. However, it can be treated in the early stages and patients in any stage can be maintained and kept comfortable long term. Fluid therapy is recommended to induce diuresis to wash out the excess uric acid. Diets low in purines and diets with a low balanced protein concentration are also suggested to decrease uric acid synthesis (6).

Given the lack of research in drug treatment of gout in reptiles, clinicians have had to rely on the human treatment protocols for gout. There are generally three goals in the treatment of gout: lower the serum uric acid concentration, promote urate excretion, and manage the inflammation (4). Allopurinol, a xanthine oxidase inhibitor purine analog, is used to reduce uric acid concentrations. Allopurinol has been used to treat gout in reptiles, but should be used with caution in patients with suspected renal or hepatic dysfunction. A study conducted with iguanas showed Allopurinol given orally at 25 mg/kg daily was able to reduce plasma uric acid levels by 41 to 45% (3). Sulfinpyrazone and Probenecid, uricosuric agents, are used to promote urate excretion. Although very little research is done in veterinary medicine, an extra label dose of

Probenecid at 250mg or 40mg/kg administered orally every 12 hours is suggested for reptile patients, based on human data (8). Colchicine and corticosteroids are used in human medicine to address to inflammation, however no research has been conducted to assess the use of Colchicine in reptile patients. Gout is known to be a painful disease in mammals, so pain relief is also recommended.

One case presentation in 2012 reported successfully treating renal gout via nephrectomy. A wild captured Monocellate cobra was observed with anorexia, imbalance of swimming and mild swelling in the distal fourth of the body. Physical examination revealed a palpable firm mass in the coelomic cavity. An exploratory surgery was performed and revealed an abnormality in the left kidney that was compressing the large intestine. Nephrectomy was performed and histopathologically identified as renal gout. The snake fully recovered within three months after surgery (10).

Case Outcome

Prior to presentation, an aspirate of the mass was taken. Urate crystals immediately formed on the slide caused by the super saturation of urate in the fluid, raising the suspicion of gout. Other differential diagnoses included a neoplastic mass, granuloma, cyst, intestinal obstruction, and abscess.

Diagnostic imaging was performed, including radiographs and ultrasound. Radiographs revealed that the mass had soft tissue opacity and measured 36mm x 35mm x 59mm.The mass was located just cranial to the vent and couldn’t be definitively associated with any specific organs in the coelom. Impacted feces were noted cranial to the mass. The lungs were also

radiographed and no lung disease or evidence of metastasis was present. On ultrasound, the heart was examined and all three chambers of the heart were identified. No apparent abnormalities were seen until the caudal third of the body when a large fecal build up was identified cranial to the mass. The mass appeared to be circumferential in the coelom and appeared to be associated with either the bowel or a kidney. The kidney was not visualized.

Toby was anesthetized with alfaxalone as the induction agent and maintained on isoflurane while an abdominal exploratory surgery was performed. He was placed in dorsal oblique recumbency and the ventral third quarter was prepped with 4% chlorhexadine solution and draped in a sterile manner. A 7 cm skin incision was made with a #15 scalpel blade paralateral to the ventral midline between 1st and 2nd row of scales, resulting in a zig-zag incision pattern to avoid incising any scales. Iris scissors were used to sharply and bluntly dissect until the coelomic cavity was accessed. Barraquer Eyelid Retractors were used to aid in visualization of the coelom. The 5cm x 3cm mass was exposed. The mass was firm, irregularly shaped, pale yellow in color, and contained numerous, approximately 1mm in diameter, foci covering the surface and extending down into the tissue on cut surface. It was encompassed in renal vasculature and contained a ureter. Meticulous dissection was used to remove the mass from the kidney lobule. Hemostasis was controlled with bipolar cautery. Small vessels branching from the renal vasculature were ligated with hemoclips allowing complete excision of the mass containing renal lobule. The area was lavaged with warm sterile saline. The subcutis was closed with 4-0 Polydioxanone suture (PDS) in a simple interrupted pattern and the skin was closed with 4-0 Nylon in a simple continuous pattern.

Diagnosis of renal visceral gout was confirmed upon histopathological examination. Throughout the sample, the renal tubules and to a lesser extent the renal glomeruli are expanded

by large radiating spiky basophilic crystalline structures. These crystalline structures are frequently surrounded by large numbers of macrophages and multinucleated giant cells. In some sections, the tissue surrounding the crystalline structures is hypereosinophilic with loss of cellular detail or is replaced by brightly eosinophilic granular material. There is increased lobulation within the renal structure, and lobules are separated by moderate bands of mature fibrous connective tissue. The collecting ducts are dilated, and frequently contain similar radiating spiky crystals surrounded by large numbers of macrophages and multinucleated giant cells. The affected portion of the kidney appeared to be completely removed. No evidence of secondary infection or of neoplasia was noted (7).

Post operatively, Toby was given Tramadol and Meloxicam to control pain and inflammation. His incision site was monitored and gently cleaned twice a day with betadine swabs for 5 days. The sutures were removed 6 weeks later since they had not detached during his shedding. Toby made a full recovery and began eating juvenile rats ten days post operatively. By February 2018, one year post operative, Toby continues to do well. He is maintained on his diet of offered mice every week and has regained most of his weight loss, weighing 570g. No waste excretion abnormalities have been noted.

Gout is a common disease occurrence in reptile patients and veterinarians with exotic patients are required to be familiar with it. This case report is designed to showcase the disease and its presentation and treatment. Continued research in the veterinary field geared toward gout and its treatment in reptiles is a necessity to fully comprehend the disease and to fully explore treatment and prevention modalities.

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