Oh No Mojo! I Can't CU!

Whitney N. Brown
Mississippi State University
College of Veterinary Medicine
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Advisor: Hayley Gallaher, DVM

Introduction:

Cystine uroliths are less frequently seen in small animals compared to struvite or calcium oxalate, and have been associated with certain breeds, neuter status, gene mutations, and diet. Breeds that are afflicted the most include the Newfoundland, English Bulldog, Dalmatian, Dachshund, and Labrador Retrievers, but can vary depending on the country.[3] In one retrospective study performed in the UK, intact male dogs were shown to be more prone to have cystine uroliths than those that were neutered and the neuter status of certain breeds were associated with cystine uroliths.[2]

As a smaller stone, cystine uroliths can make their way from the bladder into the urethra where they become lodged as the urethral diameter decreases in size. This occurs more commonly in male dogs due to a long and narrow urethra with more muscle compared to female dogs.[9] Location of an obstruction will determine which surgical technique is the best choice for treatment. The most common location for calculi to become lodged is at the base of the os penis. A majority of urethroliths can be dislodged using retrograde hydropulsion followed by cystostomy for retrieval of the calculi. In cases where the urethroliths cannot be dislodged, a scrotal urethrostomy is preferred over perineal urethrostomy due to less hemorrhage and a more superficial urethra.[9] Partial or complete obstructions can occur; however, it is complete obstructions that are a life-threatening emergency and warrant immediate attention. When urine outflow is obstructed there is an increase in pressure and dilation of the urinary tract that may result in atony of the detrusor muscle, decreased glomerular filtration rate (GFR), decreased renal blood flow (RBF), and hypoxia.[14] Hyperkalemia, azotemia, and metabolic acidosis can be seen if an obstruction is present for 24 hours or more. Hyperkalemia causes decreased contractility of the heart by decreasing the resting potential and can cause life threatening

arrhythmias. Echocardiographic abnormalities may include “tenting” of the T wave with shortening of the QT-interval with mild, prolongation of the PR-interval with widening of the QRS complex in moderate, and absence of P waves in severe hyperkalemia.[15] If a complete urethral obstruction is left untreated or goes unnoticed by the owners, renal decompensation will occur within 24 hours of obstructing and can lead to acute kidney injury.[9]

History and Presentation:

Mojo is a 4-year-old intact male Old English Bulldog who presented to MSU-CVM Surgery department on 10/10/18 for a urethral obstruction diagnosed by his primary veterinarian. Mojo originally presented to his primary veterinarian on 10/3/18 for increased frequency of urination (pollakiuria), and it was suspected he had a urinary tract infection based on radiographs and urinalysis. His primary veterinarian did not see stones present on radiographs at that time, however it was difficult to pass a 5 French urinary catheter. Mojo was then sent home on Clavamox which caused him to vomit and he was later switched to enrofloxacin. He was also prescribed metoclopramide for nausea. His owners said Mojo seemed to be doing a little better until Tuesday. Tuesday 10/9/18, Mojo presented to his primary veterinarian for pollakiuria, stranguria, and hematuria. At this visit radiographs were taken which revealed urethroliths. Intravenous crystalloid fluids and an antibiotic (unknown to owners) were administered. Attempts to retropulse the uroliths back into the bladder were made by the primary veterinarian and were unsuccessful. It was discussed with the owners that Mojo would need a scrotal urethrostomy. Mojo’s owners would like to breed him in the future and were hesitant to go forward with the procedure. Mojo was then referred to MSU-CVM for a second opinion.

On presentation, Mojo was bright alert and responsive. His mucous membranes were pink, moist, and had a normal capillary refill time of less than 2 seconds. His vitals were within

normal limits (temperature was 101.8 F, heart rate was 96 beats per minute, and respiration was 32 breaths per minute). Cardiothoracic auscultation was normal with no murmurs, crackles, or wheezes present. A rectal exam was performed to rule out benign prostatic hyperplasia or masses that would obstruct the urethra, and no abnormalities were palpated, in spite of a lack of patient compliance during this portion of the exam.

Pathophysiology:

Cystine is a dibasic amino acid and is formed by two disulfide bonded cysteine monomers.[8] In the normal kidney, cystine and other dibasic amino acids (ornithine, lysine, and arginine) are freely filtered through the glomerulus and reabsorbed in the proximal tubules via heterodimer transporter pumps.[4] Cystine solubility decreases as urine pH decreases, while the other amino acids are unaffected.[1] If the urine is acidic, the insoluble cystine becomes concentrated within the urine and stones are formed. Specific mutations of the SLC3A1 and SLC7A9 genes that code for the transporter pumps have been associated with Newfoundlands, and while some point mutations have been identified in English Bulldogs, it is uncertain whether this plays a role in cystinuria.[4] When there is a mutation of the SLC3A1 and SLC7A9 genes, increased protein within the diet, or the pH of the urine is decreased, the cystine is no longer reabsorbed and remains within the ultrafiltrate that will become urine. This dysfunction in renal absorption of cystine, will result in either cystinuria or the formation of cystine uroliths. Cystinuria, or presence of cystine crystals, does not indicate the presence of uroliths but is considered a predisposing factor to the formation of stones.[7,10] An acidic or neutral urine pH (normal is 5.5-7.5) in combination with a dysfunctional pump creates near perfect conditions for stone formation.[3]

Diagnostic Approach/considerations:

Before going to surgery, a minimum database (CBC, Chemistry, urinalysis) and diagnostic imaging were performed. His CBC was largely unremarkable with a moderate monocytopenia. His neurochemistry was also unremarkable with only a mild elevation in creatine kinase likely from the attempts to retropulse the stones into the bladder. His urinalysis revealed isosthenuria (USG of 1.008), proteinuria, significant hematuria, occasional epithelial cells, and his urine was just within the normal pH range at 7.5. No bacteria were seen within the urine sample. An abdominal FAST scan was performed which revealed a thickened bladder wall. An intravenous catheter was placed, and Mojo was sedated with dexmedetomidine, hydromorphone, and midazolam for radiographs. On radiographs, the bladder contained multiple smoothly marginated mineral opaque rounded structures of varying sizes (the largest being approximately 3.1 mm). Within the urethra along the os penis, there are three smoothly marginated mineral opaque rounded structures with the largest and most proximal being approximately 5 mm in diameter and the smallest being approximately 2.6 mm in diameter. An unremarkable chemistry and history of dribbling urine lead us to believe that the stones seen on radiographs were not completely obstructive. Electrolyte abnormalities along with a severe and life-threatening hyperkalemia are commonly seen with complete urinary obstructions if present long enough.

Retrograde hydropropulsion was then attempted using a red rubber catheter and LRS. Attempts to retropulse the stones into the bladder were unsuccessful and a red rubber catheter was sutured in place using the Chinese finger trap at the preputial orifice to allow for passage of urine throughout the night. Due to the location of the urethral obstruction, a scrotal urethrostomy was discussed with the owners. Mojo's owners expressed interest in breeding him in the future, thus leading to a reluctance to neuter. In any case of urethral obstruction, a cystotomy is

performed first to remove any cystoliths present before performing the urethrostomy. His owners elected to go forward with the scrotal urethrostomy, as long as attempts to retropulse the stones were made or an epididymal flush was performed following the removal of testicles in order to save semen.

In surgery, an approximately 4-inch incision was made to the right of the prepuce extending from the base of the prepuce cranially. The bladder was lifted out through the incision and held in place by laparotomy pads beneath it at the incision site. Two stay sutures were placed on the bladder apex to facilitate manipulation. The incision was made on the ventral surface of the bladder away from the urethra, ureters, and major blood vessels. Urine within the bladder was removed using suction and the stones in the bladder were removed using a bladder spoon. The stones were then sent out for analysis. A small section of the bladder wall was excised and submitted for aerobic and anaerobic culture and sensitivity. Various catheter sizes were placed into the urethra in an attempt to flush the stones in the urethra back into the bladder. It was suspected that the urethra was ruptured during this process. The bladder was closed in a single layer using simple continuous pattern with 3-0 Monocryl. The bladder was leak tested with warm saline through the urinary catheter and an 8 French Foley catheter was placed through the urethra and into the bladder for post-operative care. The abdominal wall was closed with a simple continuous pattern using 0 PDS suture. A simple continuous pattern was used to close the subcutaneous tissue using 2-0 PDS and the skin was closed using an intradermal pattern. Before starting the urethrostomy, radiographs were taken to confirm catheter placement and removal of the cystoliths.

A scrotal urethrostomy is performed to create a new and permanent stoma of the urethra at the level of the scrotum to allow appropriate urine flow.[9] For this procedure, the scrotum and

testicles were elevated from the body and an elliptical incision was made at the base of the scrotum. The vaginal tunics were incised, and the spermatic cords were ligated and transected. The testicles were removed and transported to the Theriogenology department for the epididymal flush. The scrotum was removed after incising the median septum. A ventral midline incision was made through the skin and subcutaneous tissue between the caudal aspect of the os penis and scrotum. The retractor penis muscle was retracted laterally to expose the urethra. With a #15 scalpel blade an incision was made into the urethral lumen over the catheter and the incision was extended with iris scissors. To ensure the stoma is of adequate size, it is recommended that this incision is extended 2.5 to 4 cm.[9] Full thickness simple interrupted sutures were placed with 4-0 Monocryl from urethral mucosa to the dermis. The subcutaneous tissue on the cranial and caudal portion of the incision was closed using a simple continuous with 3-0 Monocryl and the skin was closed with 2-0 Dermalon in a cruciate pattern.

Once the Theriogenology department received the testicles, the tails of the epididymis and ductus deferens were isolated from each testicle. Using an IV catheter, they were flushed with semen extender and four straws were obtained and frozen. The post-thaw motility was 30% and enough semen was obtained for one breeding dose.

Treatment and management:

When treating cystine uroliths, surgery is the treatment of choice and the surgical technique may vary depending on the location of uroliths. It is important to inform clients of the long-term management associated with animals that are prone to cystine uroliths. Long term management includes diet change, increasing water intake, castration, thiol containing drugs, urine alkalinizing agents and frequent monitoring as this may be a reoccurring problem. Methionine is a precursor of cysteine and can be present in high protein diets causing an

increased risk of stone formation. To prevent this, converting to diets that are restricted to 10 to 18% dry matter high quality protein will help prevent acidic urine and improve the solubility of cystine.[1] Encouraging water intake or feeding canned food to help dilute the urine and encourage urination will also help decrease the risk. As previously mentioned, some dogs have an androgen dependent cystinuria and once the source of androgens are taken away, these dogs may no longer have issues with cystinuria.[6] If the diet changes and castration does not reduce the cystinuria, thiol containing drugs such as 2-MPG and D-penicillamine can be added to the treatment regimen.[6]

2-Mercaptopropionylglycine (2-MPG, tiopronin) is a second-generation cysteine chelating agent that undergoes a thiol-disulfide bond exchange with cystine to create more soluble product. [11] D-Penicillamine is a degradation product of penicillin that when combined with cysteine creates a product that may be up to 50 times more soluble than free cystine and that does not interfere with the nitroprusside test allowing for appropriate titration of the drug using it as a marker.[11] Tiopronin adverse effects include aggression, proteinuria, thrombocytopenia, elevations in liver enzymes, dermatologic effects and myopathies.[12] These drugs are not the first thing we reach for in cases of cystinuria as they both have adverse effects. If thiol-containing drugs are needed, it is recommended that tiopronin is used first, due to the likelihood of hypersensitivity to or toxicity from the D-penicillamine. Nausea, vomiting, decreased GI absorption of minerals, fever, lymphadenopathy, and skin hypersensitivities are some of the adverse effects seen with the use of D-penicillamine.[13] Potassium citrate can be given orally to alkalinize the urine if there is no increase in pH after an appropriate diet change has occurred.[11]

Monitoring for cystinuria, urine pH, and imaging are important for the long-term management and prevention of cystine uroliths. Urinalysis should be performed every 3 to 6

months to determine if dietary changes are increasing the pH and the urine specific gravity is 1.020 or lower. Urine nitroprusside can be used as a screening test every 3-6 months to determine if the concentration of cystine within the urine is elevated, however some drugs such as ampicillin and sulfur containing drugs can give a false positive.[6] The recurrence rate for cystine uroliths is high for most patients and because they are marginally radio-opaque compared to struvite and oxalate, contrast studies or ultrasounds may be needed every 6 months to a year in order to catch early uroliths.[6]

Case outcome:

After surgery, Mojo was placed on fluid therapy, pantoprazole, sucralfate, maropitant citrate, carprofen, and Unasyn. His urine production was quantified every 4 hours and remained over 1 ml/kg/hr until taken off intravenous fluids, at which time they were restarted. After regurgitating multiple times, the constant rate infusion of fentanyl was discontinued, and he was placed on a constant rate infusion of metoclopramide for its antiemetic effects. The first night after his surgery, Mojo appeared painful and was placed on constant rate infusion of 2% lidocaine to provide some analgesia.

One of the most common complications associated with scrotal urethrostomies is hemorrhage. This is due to the disruption and engorgement of the highly vascular corpus spongiosum that surrounds the urethra and closely underlying corpus cavernosum.[16] Mojo's urethrostomy site began to hemorrhage more than expected at one day post-op, so a packed cell volume was performed. His packed cell volume was lower than normal at 21% which prompted close monitoring. Mojo was blood typed in preparation for the possibility of transfusion if he took a turn for the worse. Excitement and dog aggression while in the ICU may have contributed to the engorgement of these tissues causing hemorrhage, so acepromazine was added to his

treatments for its calming effects. Fortunately, his packed cell volume started to increase over the next few days, and no intervention was necessary.

Mojo was discharged on October 19, 2018, with instructions to warm pack his incisions, restrict activity, keep an Elizabethian collar on until incision sites were healed, and to feed Hill's C/D until the stone analysis results were back. Although no bacteria were cultured, he was sent home with Clavamox to treat any bacteria that may have been introduced through his catheters or surgery and carprofen for pain management. On October 26, 2018, Mojo's stone analysis results from the Minnesota Urolith Center were in and results concluding his uroliths were made of pure cystine. On his two and three week recheck appointments, his urethrostomy site and incisions appeared to be healing well. On February 29, 2019, Mojo presented to the Small Animal Internal Medicine department for recheck urinalysis and gaining weight. At that time, he was receiving 1 cup of Hill's C/D, 1 Milk Bone, and 1 Greenies per day with 1 cup of chicken every 2 days. His urine pH was still within normal limits, but lower than previously. During this visit he was placed on Hill's U/D, which is specifically formulated for the dissolution and prevention of cystine uroliths.

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