Ur-ine Trouble

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Introduction

Proliferative urethritis (PU) is a rare condition that causes inflammation and proliferation of the urethra, often leading to a partial or complete urinary obstruction [1,3]. Therefore, clinical signs may include dysuria, stranguria, pollakiuria, and hematuria [1]. Due to the presenting symptoms and the appearance of the involved tissue, these cases are often misdiagnosed as neoplasia such as transitional cell carcinoma [3]. There are no inherited or genetic links proven, but associations have been suggested in a few studies [1,3]. One study suggested that there was an overrepresentation of German shepherds [1] and a more recent study claimed that in their experience, this disease only affects females [3]; however, there is not enough evidence to support these claims.

History

At the time of presentation on July 29, 2020, Ziva was a 3-year-old spayed female German Shepherd that was referred to MSU-CVM Emergency Service for overflow incontinence. The owner's son noticed that Ziva was dribbling urine and took her to a veterinarian where she received a Convenia injection for a suspected urinary tract infection. On July 21st, Ziva returned to another veterinarian for weight loss and continued inappropriate urination in the house. Blood chemistry revealed that Ziva was azotemic and abdominal radiographs showed a severely distended urinary bladder. Ziva was sent home on prazosin and she returned to the hospital the following day. A urinary catheter was placed, and she was treated with intravenous fluids and enrofloxacin was initiated. On July 23rd, she was switched to marbofloxacin and maintained on intravenous fluids and a urinary catheter. The urinary catheter was removed on July 24th but Ziva was still unable to urinate. Due to some mucoid vulvar discharge, the primary care veterinarian recommended an ovariohysterectomy. The surgery was

performed that night and the urinary catheter was replaced and maintained overnight. On July 25th, the azotemia resolved, diazepam was initiated, a 24-hour injection of Metacam was given and the prazosin dose was increased from 2mg to 5mg orally every eight hours. Ziva's urinary catheter was removed, and she was discharged on July 27th. Her last normal urination, prior to presentation, was on July 27th after the removal of the urinary catheter. She was still unable to urinate on July 28th and was referred to MSU-CVM by the primary care veterinarian.

Presentation

Upon presentation, Ziva was bright, alert, and responsive. She weighed 31.6 kilograms with a body condition score of four out of nine and had a temperature of 102.4°F. She was adequately hydrated with pink and moist mucous membranes and a capillary refill time of less than two seconds. She had strong, synchronous femoral pulses and had a heart rate of 112 beats per minute. She had an elevated respiratory rate of 60 breaths per minute with a normal respiratory effort, therefore the increased rate was likely due to anxiety. Her heart and lungs auscultated normally with no murmurs, arrhythmias, crackles or wheezes detected. Upon abdominal palpation, Ziva was tense, but non-painful and had a moderate to severely enlarged urinary bladder. She had a healing abdominal incision, consistent with her recent ovariohysterectomy. The incision appeared clean, dry, and intact. An approximately one by one centimeter soft, smooth mass was located cranial to the spay incision. She was ambulating normally on all four limbs and no pain was elicited on spinal palpation. All peripheral lymph nodes were smooth, soft, and symmetrical. She had a moderate to severely thickened urethra upon rectal palpation. The remainder of her physical exam, neurologic exam, and triage parameters were unremarkable.

Diagnostic approach

In the case of urinary obstruction in a dog, differential diagnoses may include urolithiasis, urethral stricture, neoplasia, proliferative urethritis, cystitis/urethritis, neurologic impairment, prostatic enlargement, or a congenital anomaly[5]. A rectal exam should always be performed to evaluate the prostate and urethra[5]. Due to Ziva's age, gender, and normal neurologic exam, some of these diagnoses can be ruled out. The next diagnostic steps should include a complete blood count, blood chemistry, urinalysis, and urine culture to evaluate kidney function and to screen for an infection. With deeply embedded infections, fluorescence in situ hybridization (FISH) of urethral tissue can be used to identify the presence of bacteria[1]. Radiographs and ultrasound are useful in identifying uroliths, masses, and thickening of the bladder and urethra. A cystourethroscopy is the next appropriate step to visualize the urethra and obtain a biopsy. Based on the appearance of abnormal tissue with frond-like projections on urethroscopy and the clinical signs, a presumptive diagnosis of proliferative urethritis can be made; however, transitional cell carcinoma and proliferative urethritis can appear remarkably similar on urethroscopy, and histopathology is required to confirm the diagnosis [1].

Following the physical examination, a renal panel revealed a mildly elevated creatinine and mildly decreased albumin. Urine was collected via cystocentesis and a urinalysis revealed a moderate elevation in red blood cells, mild elevation of white blood cells, and a specific gravity of 1.027. Ziva was sedated, and a urinary catheter was placed without complication. Ziva was maintained on closed urinary connection system overnight. Due to anxiety, Ziva was given trazodone overnight and she was transferred to the MSU-CVM Internal Medicine service on July 30, 2020. An abdominal ultrasound revealed a severely distended urinary bladder with a thickened bladder wall, as well as a distended proximal urethra with smooth, undulating mucosal

margins. The renal pelves were moderately dilated bilaterally. Due to the lack of urinary stones on abdominal radiographs (performed by the primary care veterinarian), the findings on ultrasound, and the thickened distal urethra found on rectal palpation, a urethrocystoscopy was recommended as the next appropriate diagnostic step.

Ziva was anesthetized later that day and urethrocystoscopy was performed. Upon entry of the scope into the urethral lumen, numerous frond-like projections were appreciated. The abnormal tissue began at the external urethral orifice and extended approximately three centimeters cranially into the urethral lumen. No other abnormalities were found in the remainder of the proximal urethra or urinary bladder. Tissue samples were collected for cytology, biopsy, culture and FISH. The culture was negative for aerobic and anaerobic growth and the FISH sample was not submitted. Ziva's cytology revealed epithelial proliferation with mild to moderate cell atypia. The biopsy of the urethra revealed moderate to marked multifocal eosinophilic, plasmacytic, and neutrophilic urethritis with multifocal papilliferous mucosal hyperplasia and lamina proprial fibrosis. Furthermore, the urinary bladder wall biopsy revealed moderate multifocal eosinophilic, plasmacytic, and lymphocytic cystitis with moderate lamina proprial fibrosis. Taking these results into consideration, along with Ziva's age and clinical signs, a definitive diagnosis of proliferative urethritis was made.

Pathophysiology

Proliferative urethritis is a mysterious condition with an unproven etiology [1,3,4]. Because the condition is extremely rare, there are very few opportunities for research and the studies we do have are retrospective studies with small sample sizes. PU was previously described as granulomatous urethritis due to the presence of macrophages found on histopathology [1,3]. The inflammatory tissue itself may vary by case and can be granulomatous but is not always[1]. The

inflammation may also be lymphocytic, plasmacytic, neutrophilic, and/or eosinophilic in nature[1,3,4]. There is speculation that the growth of inflammatory tissue is instigated by immune mediated disorders, chronic or deep infections, or possibly a combination [1,3,4]. One study hypothesized that deep bacterial infection leads to urethritis and the subsequent proliferation of inflammatory tissue, but the study was unable to prove the hypothesis [1].

A common sequela to proliferative urethritis includes an obstructive uropathy[3]. The proliferative inflammatory tissue fills the lumen of the urethra causing a partial or complete obstruction. Clinical signs associated with obstruction include stranguria, pollakiuria, dysuria, overflow incontinence, and/or anuria[2]. Because the urine is unable to flow freely, it backs up into the urinary bladder[2]. The bladder becomes overly distended and the bladder wall may become ischemic[2]. The overly stretched smooth muscle fibers of the detrusor muscle cause the tight junctions between cells to separate leading to detrusor atony[2]. Detrusor atony leads to urine retention because the bladder can no longer contract normally[2].

The blockage of urine flow may also cause urine to back up into the ureters and kidneys leading to stretching of the ureters causing hydroureter as well as damaging the renal parenchyma by causing pressure atrophy leading to hydronephrosis [2]. Continual partial or complete obstruction leads to a decline in renal function such as a decrease in all of the following: ability to concentrate urine, acidifying ability, glomerular filtration rate, and renal blood flow [2]. This decreased renal function causes a post-renal azotemia as well as a hyperphosphatemia, hyperkalemia, hyponatremia, hypochloremia, and metabolic acidosis [2]. If left untreated, a complete urinary obstruction is fatal within three to five days because of the body's inability to dispose of waste products such as potassium in the urine[2]. The resulting hyperkalemia and metabolic acidosis may lead to death [2].

Treatment and Management

After completion of the urethrocystoscopy exam, a urinary catheter was replaced with a closed collection system. Ziva was started on gabapentin and trazodone was continued. After the return of the histopathology report on July 31st, azathioprine and prednisone were begun. Ziva was maintained on the urinary catheter and closed collection system for three days to allow time for a decrease in the inflammation of the urethra. The urinary catheter was removed at 10am on August 2nd to challenge Ziva's ability to void urine. Ziva was walked frequently and her bladder was measured with ultrasound after urination. She urinated well at 3pm with a good stream and she urinated again at 9pm but with a poor quality stream so prazosin was restarted. At midnight, her bladder exceeded 12mls/kg upon measurement with ultrasound; therefore, the urinary catheter was replaced on August 3rd. Bethanechol and diazepam were started on August 4th. Due to quickly decreasing monetary funds and the possible outcome of euthanasia, the prazosin was increased from 2mg to 5mg orally every eight hours with the owner's understanding that this dose could cause hypotension and damage major organs such as the kidneys. The remainder of the medications were continued at the previously prescribed dosages. After several days, the urinary catheter was removed once again on the morning of August 7th. Ziva urinated well throughout the day about every two to four hours and she would urinate multiple times outside. Her urine stream was pulsating but strong and she was able to void her bladder down to 3mLs/kg. Overnight, her bladder reached 12mLs/kg, but she was still able to void urine. On the morning of August 8th, Ziva's bladder decreased to 4.8mLs/kg after urination. Due to monetary constraints and Ziva's ability to void urine, she was sent home with instructions to seek veterinary attention immediately if she ceased to produce urine at any time. The overall goal of Ziva's treatment plan was to wean her off the prednisone over a month, and then determine the

lowest effective dose of azathioprine. Due to the risk of hypotension, the prazosin was lowered to a safer dose range prior to discharge, but with understanding that it could be titrated to effect if Ziva was unable to urinate.

The goal of treatment for proliferative urethritis is to decrease or eliminate the inflammation/abnormal tissue and re-establish urethral patency and maintain patient comfort. Both medical management and surgical interventions have been attempted to treat this condition and all have varying outcomes[1,3]. Medical management involves antibiotics if indicated by culture or FISH, an anti-inflammatory such as non-steroidal anti-inflammatories or glucocorticoids, and/or an immunosuppressive agent[1,3]. A case report by Hostutler et al on two dogs diagnosed with PU suggested that, "the persistence of urethral inflammation might prevent antibiotic penetration into affected urinary tissues." He went on to suggest that following antibiotics with an immunosuppressive agent may aid in the resolution of clinical signs and resolve urethral inflammation[4]. Additional medical management options include medications for urethral relaxation such as prazosin, an alpha-adrenergic blocker[3]. The most commonly used immunosuppressive agent appears to be azathioprine, as the majority of cases in the retrospective study by Emanuel et al and the two cases in the case report by Hostutler were treated with azathioprine with some success[3,4].

The most successful surgical treatments for urethral obstruction secondary to proliferative urethritis include balloon dilation and urethral stent placement followed by medical management with an immunosuppressive agent and an anti-inflammatory[3]. Surgical debulking was reported in one case by Emanuel et al but was unsuccessful in alleviating the obstruction[3]. An additional reported surgical intervention for urethral obstruction included vaginourethroplasy[4]. One study concluded that surgical interventions were more successful than medical management alone and

urethral stenting appeared to have better long-term success in comparison to balloon dilation[3]. Urethral stents are normally placed using fluoroscopy but have been shown to be successful with digital radiography[5]. Potential complications of urethral stent placement include urinary incontinence, hematuria, and dysuria[3,5]. In Ziva's case, the section of affected urethra started at the urethral orifice and extended cranially. Therefore, stenting of the affected area would most likely have rendered her incontinent.

Case Outcome

Ziva was discharged on August 8th, 2020 without a urinary catheter and instructions to monitor her urination closely. Medications sent home included prednisone, azathioprine, prazosin, diazepam, gabapentin, and trazodone. The primary care veterinarian agreed to take over Ziva's care with consultation of the MSU-CVM Internal Medicine Service. A repeat complete blood count, blood chemistry, and urinalysis was recommended on August 14th, 2020. In the following days, Ziva continued to urinate without complication. Ziva returned to the primary care veterinarian and the lab results were forwarded to MSU-CVM on August 20th. The blood chemistry revealed severely elevated liver enzymes. At the time of recheck, Ziva was polyuric and polydipsic and the owner reported that she was leaking urine when she slept, but she was still voiding urine outside without difficulty; therefore, these complications were suspected to be side effects of prednisone. Due to the elevated liver enzymes, the azathioprine was decreased, and prednisone was continued at the original dose. It was recommended to recheck the blood chemistry to re-evaluate the liver enzymes. The primary care veterinarian saw Ziva again on November 4th and she was doing well. Therefore, it was advised that the immunosuppressives continue to be tapered by 25% every three to four weeks. Ziva's

medications were discontinued in late November 2020. Since then, Ziva has been urinating well and has made a full recovery.

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