Molly Pop Star: From Misfortune to Marvel

A Case of Ectopic Ureters in the Canine Patient

Presented by:

Hannah L. McCurdy

Mississippi State University

College of Veterinary Medicine

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Advisors:

Patty Lathan, VMD, MS, DACVIM

Katie Cooley- Lock, DVM, MS

Introduction

Ectopic ureters are most common congenital cause of urinary incontinence in dogs.[1] This rare congenital malformation occurs when one or both ureters enter the bladder in an incorrect anatomic position.[2] The ureteral entrance is normally in the trigone of the bladder, but in the case of ectopic ureters, the opening is more caudal than normal, entering in the neck of the bladder, urethra, uterus, vestibule, or vagina.[2,6] The diagnosis of ectopic ureters is typically in young female dogs, with a median age of 10 months, but may present at any age with males presenting later, with a median age of 24 months.[1] Females account for 89-95% of dogs diagnosed with ectopic ureters.[1] Clinical signs of ureteral ectopia are usually continuous or intermittent urinary incontinence, with most dogs exhibiting normal voiding patterns if the ureteral ectopia is unilateral since the remaining normal ureter is emptying into the bladder; however, if both ureters are ectopic, normal urination may not occur [1,9]. Urinary incontinence in a young dog is not in itself diagnostic of ectopic ureters.[3] Physical examination of dogs with urinary incontinence due to ectopic ureters, or other causes of urinary incontinence, may reveal urine scalding or staining of the perivulvar or preputial regions.

There are two types of ectopic ureters described in the canine patient: intramural and extramural, with intramural being much more common, with reports stating that more than 95% of ectopic ureters in dogs are intramural. [2,6] Intramural ectopic ureters enter the bladder wall in the proper location; however, after their entry, they track submucosally through the bladder wall, ultimately opening distal to the internal urethral sphincter.[2] On the other hand, extramural ectopic ureters are more common in feline species, although the diagnosis is still quite rare.[8] Although the appearance of ectopic ureters is more common in female dogs than male dogs, there is not as much of a defined sex-distribution in cats. [8] The presence of urinary incontinence

in male dogs is much less frequent than in female dogs; however, male cats with ectopic ureters are often incontinent.[8] Ectopic ureters may be unilateral or bilateral, with studies showing a fairly equal distribution between the two.[2,4,6]

History & Presentation

Molly Pop Star is a 2 year old female spayed Labrador retriever who presented to MSU-CVM Internal Medicine on June 27, 2018 for progressively worsening urinary incontinence following an ovariohysterectomy performed in March of 2017. Molly's family veterinarian prescribed diethylstilbestrol (DES), a synthetic estrogen, for the urinary incontinence, but due to possible side effects, it was discontinued and a trial of phenylpropanolamine (PPA), a sympathomimetic selective alpha agonist very commonly used for dogs with hormone responsive urinary incontinence, was administered. After one week of PPA administration, no improvements were noted and the DES was reinstituted. Improvement, but not resolution, of the urinary incontinence was noted while Molly was on the DES with the owner describing a waxing and waning of clinical signs. On presentation to MSU-CVM, Molly was bright, alert and responsive. Her physical examination was within normal limits with a temperature of 102.8 degrees Fahrenheit, heart rate of 132 beats per minute, and a panting respiratory rate. Molly weighed 27.5 kilograms. No abnormalities of the heart or lungs were noted upon chest auscultation.

Diagnostic Approach

A CBC, serum chemistry, urinalysis and urine culture were performed. Molly's CBC revealed a mild thrombocytopenia 146 K/ul (160-650 K/ul) with a normal serum chemistry, urinalysis, and negative urine culture and sensitivity. Given the association of urinary

incontinence following Molly's spay, a presumptive diagnosis of urethral sphincter mechanism incompetence was made. It was recommended that Molly start PPA and that she slowly be weaned off of the DES over the next 30 days with the possibility of it being reinstituted in the future if deemed necessary. Molly's owner was informed that additional diagnostics may be warranted if her clinical signs did not improve or resolve. A one month recheck was scheduled with MSU-CVM.

One month later, July 25, 2018, Molly presented to MSU-CVM again for progressive worsening of her urinary incontinence. Molly's physical exam revealed that Molly's vulva was rotated cranioventrally, but there was no urine staining or scalding in the perivular area. The frequency of administration of PPA was increased and Molly was scheduled for a recheck in one month.

At the next recheck, August 22, 2018, Molly's owner expressed that Molly's urinary incontinence had remained static. It was decided that Molly's PPA dose and frequency were to remain the same for another month. Molly returned to MSU-CVM on September 21, 2018 for worsening urinary incontinence. At this visit, a urinalysis was performed, which was within normal limits, and Molly was scheduled for a vaginourethrogram and cystoscopy the next week. Her owners were instructed to continue Molly on PPA and DES until this time.

On October 5, 2018, Molly returned to MSU-CVM for cystoscopy and vaginourethrogram. Her owner reported no improvement in Molly's incontinence since her last visit. Physical examination was unremarkable and routine bloodwork was performed, deeming Molly healthy and able to undergo anesthesia. Molly was premedicated with dexmeditomidine and hydromorphone and induced with propofol. Molly was placed in dorsal recumbency, maintained on isoflurane and a cystoscopy was performed. A rigid scope was used to visualize a

paramesonephric duct remnant upon entrance into the vestibule of the vagina, which partially covered the vaginal orifice. Prior to entry of the urethral orifice, there was a large, anatomically abnormal opening dorsal to the urethral orifice. It was noted that upon entry into the urethra that the urethral folds were normal; however just distal to the trigone, another anatomically abnormal opening was noted dorsally. Visualization of the bladder revealed ureteral papilla at the 7 and 4 o'clock positions and urine jets were noted. The ureteral papilla at the 7 o'clock position, or the right ureteral papilla, was noted to be somewhat larger after exploration of the opening within the urethra, just distal to the trigone, with urine noted to be exiting this opening as well. At this time, Molly was suspected to have two ectopic ureters as well as a paramesonephric duct remnant. She was taken to radiology for a vaginourethrogram while still under anesthesia following her cystoscopy. Ioversol injection, contrast agent,was diluted 1:1 with sterile saline and 100mL of this solution was injected into the urinary bladder via a foley catheter in 15mL aliquots. The vaginourethrogram revealed a pelvic urinary bladder, a very common finding in dogs with urinary incontinence and an abnormally dilated right ureter, which is the most frequently reported radiographic abnormality in dogs with ureteral ectopia, particularly intramural ureters that are displaced into the vagina or urethra (3). This dilation is a result of the mucosal and submucosal layers of the tunnel that the intramural ureter is going through create a roof, intermittently obstructing outflow from the ureter, causing hydroureter (3). Molly was scheduled to return on October 10, 2018 for contrast and guidewire placement of her ectopic ureters to determine if they were intra or extramural, as well as laser therapy of the paramesonephric duct remnant and possible laser therapy or surgical correction of the ureteral ectopia depending on if they were intramural or extramural, respectively.

On October 10, 2018, Molly presented to MSU-CVM and was BAR, with a normal TPR, and her heart and lungs auscultated normally. A Big 4 was collected and the results were as follows: PCV: 52% (35-55%), TP: 6.2g/dL (5.5-7.5), glucose: 106mmol/L (79-126), and azostix 5-15mg/dL (7.0-26), all of which were within normal range. Molly was pre-medicated with dexmedetomadine and hydromorphone, induced with propofol, and maintained on isoflurane, the same drug protocol as she had received less than one week prior. She was taken into the operating room for her cystoscopy and laser treatment; however, after being under anesthesia for a short amount of time, Molly's pulses were unable to be felt and a heartbeat could not be auscultated. Cardiopulmonary resuscitation was started immediately and continued for around two minutes. Molly was administered atropine and epinephrine to stimulate the heart, as well as atipamezole and naloxone to reverse her premedications. Shortly thereafter, a heartbeat was noted and Molly was taken to ICU to recover from anesthesia. While in ICU, Molly was monitored via a continuous ECG for several hours where intermittent ventricular premature contractions where noted temporarily with resolution within 60 minutes. Molly was deemed to be neurologically appropriate; however, she continued to be tachycardic for a short amount of time during recovery due to drugs administered during CPR. Thoracic radiographs were performed to assess for injury to the ribs and lung contusions due to the performance of CPR and of which none were found. An echocardiogram was performed the following day which revealed a clinically insignificant mild regurgitation of the pulmonic valve. A 6 lead electrocardiogram revealed no issues with electrical conduction of the heart. Molly was discharged with instruction to resume her previously prescribed medications, PPA and DES, allow her heart and lungs to recover from the trauma of CPR, and return in 2 to 3 weeks for the procedure to be attempted again.

On October 30, 2018, Molly returned to MSU-CVM for guidewire placement of the ectopic ureters, as well as either laser treatment or surgical correction of the ureteral ectopia. A thorough physical examination was performed. A small animal anesthetic profile revealed no abnormalities other than a mildly elevated BUN at 29mg/dL (8-24mg/dL), which was not of concern. The following day, October 31, 2018, Molly was routinely anesthetized with acepromazine and butorphaol, induced with alfaxalone, maintained on isoflurane, and a lumbosacral epidural with bupivacaine was administered. Via cystoscopy, a guidewire was inserted into the ectopic ureter near the bladder opening and a catheter was placed around the guidewire before the guidewire was removed. Contrast was injected into the catheter which verified that the ectopic ureter was going to the right kidney. The same procedure was performed on the left ureter, as well as the abnormal opening by the vagina. The other ectopic ureter at the vagina was not patent and did not connect to the kidney. A laser wire was introduced through the endoscope and the tissue between the right intramural ectopic ureter and bladder lumen and was lasered with urine visualized exiting the new opening. The laser was also used to cauterize the extra tissue making up the paramesonephric duct remnant. Bupivacaine diluted in a 1:1 dilution was infused into the bladder and near the vagina for local pain control. Molly recovered uneventfully from her procedure. She was discharged with instructions to be monitored for continued dribbling and urine scalding. She was sent home with Clavamox and gabapentin. Molly's owners were instructed to bring Molly back for a recheck in two weeks and at that time, it will be determined if adding in her previous medications (PPA and DES) will be necessary.

Pathophysiology

As ectopic ureters are the most common congenital cause of urinary incontinence in dogs, the discussion of the embryologic development associated with this anomaly is of importance in

the understanding of ectopic ureters and their formation in the dog. Research has shown that "vertebrates have one of three distinct excretory organs: the pronephros, mesonephros, and metanephros."[1] Primitive fish and amphibians may utilize the pronephros and mesonephros, respectively, but mammals, as well as birds have developed the metanephros.[1]

As urogenital development is taking place, each of these (pronephros, mesonephros, and metanephros), succeed each other, and parts of each may be retained in the developing embryo.[1] In mammals, only the duct of the pronephros is retained as the mesonephric duct, which is active in the canine fetus, but becomes vestigial in females, while the mesonephric duct is retained as the deferent duct in males.[1] The metanephric duct, derived from a bud of the distal mesonephric duct near the cloaca will eventually become the ureter, thus revealing that the mesonephric and metanephric ducts share a common duct and opening when the bladder is first forming.[1]

As development continues, the metanephric duct grows towards the tissue that forms the kidney.[1] The common duct is absorbed as the bladder continues to develop, resulting in the meso and metanephric ducts forming their own separate openings.[1] As the fetus grows, the mesonephric ducts track more caudally and in normal development, open on a prominence on the dorsal urethral wall, and the ureteral openings remain in the bladder.[1] If the origin of the metanephric duct is more cranial on the mesonephric duct than it should be, it will not be able to establish its own separate opening into the bladder, because it is unable to reach.[1] This results in the metanephric duct being taken caudally with the mesonephric duct, opening much further caudal than normal, most commonly in the urethra of females and males, but has the potential to open in the bladder neck of both males and females, and the deferent duct in males.[1] Urinary incontinence in dogs with ectopic ureters occurs because of the urine drainage distal to the

trigone of the bladder and the internal urethral sphincter or a physical disruption of the musculature of the internal urethral sphincter caused by an intramural ureter.

In the canine, fusion of the paramesonephric, or muellerian duct is responsible for the formation of the uterus, uterine tubes, cervix, and vagina, while the urogenital sinus develops into the urinary bladder, urethra, and vestibule[10]. According to Burdick, “the caudal aspect of the fused ducts projects into the urogenital sinus, becoming canalized, and forms the vaginal opening with a membrane resulting in the hymen.”[10] Abnormal development during this embryological process can result in various abnormalities of the urinary tract, including a persistent hymen, vestibulovaginal stenosis, vaginal segmental hypoplasia, or in Molly’s case, a persistent paramesonephric septal remnant.[10]

A persistent paramesonephric septal remnant is noted when tissue extends cranially from the vestibulovaginal junction, and is <1cm in thickness, but cannot be perforated by digital pressure.[10] The clinical significance of paramesonephric septal remnants is not immediately clear as it is an incidental finding in some dogs, but in others may develop a plethora of clinical signs such as persistent urinary incontinence, vaginal pooling of urine, dysuria, chronic recurring urinary tract infections, infertility, difficulty breeding naturally, vaginitis, and dystocia, among others.[10] There is no reported genetic or breed disposition and the overall prevalence is unknown, as most dogs are never bred, spayed early in life, and may never exhibit clinical signs.[10] According to Burdick, “These defects often occur concurrently with other congenital malformations and were recently reported in 93% of female dogs with ectopic ureters.”[10] In patients who have numerous congenital malformations, it is difficult to determine the actual clinical implications that a paramesonephric septal remnant has in and of itself.[10]

Treatment & Management

As previously stated, ectopic ureters are classified as either extramural, or intramural, with the latter being much more common in the canine. Correction of extramural ectopic ureters historically has been surgical via a ventral midline incision, exposing these ectopic ureters that completely bypass the bladder neck. These ureters are then ligated distally and a new ureteral opening is made in the proper anatomic position in the bladder and the ureteral reimplantation or an end-to-side neoureterocystostomy is performed at this location.[12] Similarly, surgical correction of intramural ectopic ureters has historically required a ventral midline cystotomy, which exposed the bladder lumen, and a side to side neoureterocystotomy was typically performed. This consisted of a new ureteral orifice being made in the bladder, at the proper anatomic position, and the distal segment of the ectopic ureter ligated; however, recanalization is possible and incontinence can reoccur.[12]

In recent years, cystoscopic guided laser ablation has become the preferred method for treating intramural ectopic ureters by using a laser fiber to incise the tissue that separates the ectopic ureteral lumen from the lumen of the bladder or urethra.[12] Reports have shown cystoscopic guided laser ablation to have results similar to surgical intervention; however, this technique does present advantages in that it diminished postoperative pain and hospitalization time, and can be performed on an outpatient basis.[12]

Various treatments for paramesonephric septal remnants have been attempted over the years, with most being done with invasive surgery, such as episiotomy for surgical transection of the vaginal septum, vaginoplasty, vaginal resection and anastomosis with a pelvic osteotomy, and vaginectomy; however, surgical correction of these malformations resulted in severe complications, such as pollakiuria, dysuria, vaginal bleeding, iatrogenic damage to urethra, neurologic damage, urinary incontinence, urethral or colonic obstruction from scar tissue, among

other things.[10] In more recent years, endoscopic guided laser ablation for the treatment of these malformations has been implicated as a noninvasive alternative to surgery.[10] Endoscopic guided laser ablation is valuable both as a diagnostic and therapeutic tool for paramesonephric septal remnants.[10]

Many dogs who undergo surgical or laser treatment of ectopic ureters remain incontinent. A study published by the Journal of the American Animal Hospital Association stated that 50-69% of dogs surgically managed remained incontinent post operatively.[4] This is compared to a study published in the Journal of the American Veterinary Medical Association stating that the long term urinary continence rate following cystoscopic laser ablation alone was 47%, with numbers reaching 77% with the addition of medical, cystoscopic, or surgical interventions, since intramural ectopic ureters can tunnel submucosally and disrupt the internal urethral sphincter, the addition of certain medications, such as phenylpropanolamine, and diethylstilbestrol are often used in cases of treated ectopic ureters and continual incontinence.[6] Due to the fact that Molly was continent prior to being ovarectomized and incontinence after, it is hypothesized that while intact, there was enough estrogen present in Molly's body that her sphincters were able to work much more effectively, resulting in no noticeable leakage; however, after Molly's spay, the urinary incontinence was noted due to the drop in estrogen.

Outcome

Molly was discharged from MSU-CVM Internal Medicine on November 1, 2018, the day after cystoscopy guided laser ablation of her ectopic ureter and paramesonephric duct remnant. Molly's owners report that she has been completely continent since surgery and is doing great at home with no medications.

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