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Retrospective study of proliferative urethritis in dogs: Clinical presentation and outcome using various treatment modalities in 11 dogs

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Abstract

Background: Proliferative urethritis (PU) is an uncommon inflammatory and infiltrative disease of the urethra in female dogs, often associated with urinary tract infection (UTI). It typically presents with evidence of urethral obstruction (UO).

Objectives: Identify clinical features in dogs with PU and determine outcome after different treatment modalities.

Animals: Eleven client-owned dogs.

Methods: Medical records of dogs with histopathologic diagnosis of PU from 2011 to 2020 were retrospectively evaluated, including information on clinical pathology, imaging, and histopathology. Outcomes of various treatment modalities were recorded and compared. Long-term urethral patency (>6 months) was considered treatment success.

Results: All dogs were female and presented with UO. Eight (73%) had a history of UTI. Ten of 11 survived to discharge and were used for long-term data collection. Seven of 10 (70%) were treated using an effacement procedure (balloon dilatation [BD], stent, or both) and 6/7 (86%) achieved long-term urethral patency (>6 months). Seven of 10 had UO recurrence after their first procedure, including 3/3 (100%) that did not have effacement and 4/7 that did (57%), at a median of 101 days and 687 days, respectively. After effacement, the duration of patency was longer for those treated using a stent than BD alone (median, 843 days and 452 days, respectively).

Conclusions and Clinical Importance: Proliferative urethritis is a recurrent disease often associated with UTI. The best outcome of long-term urethral patency occurred after lesion effacement, either by BD or stenting. Future prospective studies should determine the impact of immunosuppressive treatment.

Abbreviations: BD, balloon dilatation; FISH, fluorescence in situ hybridization; PU, proliferative urethritis; RCMS, retrievable covered metallic stent; SEMS, self-expanding metallic stent; TCC, transitional cell carcinoma; TNTC, too numerous to count; UO, urethral obstruction; UTI, urinary tract infection.

KEYWORDS
effacement, proliferative urethritis, urethral obstruction, urethral patency

1 | INTRODUCTION

Proliferative urethritis (PU) is an uncommon, inflammatory, and infiltrative disease of the urethra.[1-5] This condition often is misdiagnosed as urinary tract neoplasia based on its proliferative appearance and obstructive nature.[1,2] Dogs with PU typically are female, and are presented for evaluation of pollakiuria and stranguria, most commonly associated with partial or complete urethral obstruction (UO).[1-3,6] The underlying cause has not been clearly elucidated, but it is believed to occur frequently with urinary tract infection (UTI) and may be secondary to immune-mediated inflammation of the lower urinary tract.[1-4] In a recent study, more than half of histologic samples from patients with PU were fluorescence in situ hybridization positive (FISH+) for adherent or adherent and invasive bacteria.[4]

Historically, similar non-neoplastic obstructions were described as granulomatous urethritis.[1,2] In the largest study on benign UO reported, 10 of 41 dogs were histologically diagnosed with granulomatous urethritis.[2] Urethral biopsy specimens from these dogs were characterized by clusters of lymphocytes, plasma cells, and macrophages with smaller numbers of neutrophils.[2] Another report of 2 female dogs proposed that this condition should be renamed proliferative urethritis, as a more accurate histologic and gross description of the condition.[1] Cystoscopically, cylindrical masses or frond-like lesions with fingerlike projections protrude into the urethral lumen, giving rise to the term PU.[1,4]

Options for medical management of PU include anti-inflammatory drugs such as nonsteroidal anti-inflammatories or corticosteroids, immunosuppressive agents such as corticosteroids or azathioprine, urethral relaxants such as alpha-adrenergic blockers, and antibiotics if an infection is documented or suspected. Dogs with PU most often are presented with concurrent UO and require effacement of the lesion, using either balloon dilatation (BD) or urethral stent placement, to prevent acute reobstruction and achieve the best clinical outcome.

In our experience, PU is a condition seen only in female dogs, and most often is associated with concurrent or historical UTI and urethral outflow tract obstruction. The lesion often is diffuse throughout a large portion of the urethra, resulting in circumferential narrowing or stenosis. Interventional options, such as urethral stent placement, have been reported to be successful in a small number of cases.[7,8] Our objective was to retrospectively evaluate dogs with histopathologically confirmed PU and report clinical presentation, imaging findings, and therapeutic outcomes using various treatment modalities. Our hypothesis was that the outcome of long-term urethral patency would be best achieved when the UO was effaced, either using BD or a urethral stent (temporary or permanent).

2 | MATERIALS AND METHODS

2.1 | Case selection

Medical records of dogs diagnosed with PU at The Animal Medical Center, New York between March 2011 and January 2020 were reviewed. Information on clinical pathological and microbiologic testing (CBC, serum biochemistry, urinalysis, and urine bacterial culture and sensitivity), abdominal imaging (abdominal ultrasonography, abdominal radiography, and fluoroscopy), cystourethroscopy, and histopathology of the lesion was retrieved. All animals diagnosed with PU by histopathology had slides reviewed by a single board-certified veterinary pathologist (T. Donovan) to confirm the diagnosis.

2.2 | Medical record review

Data was retrospectively collected from the Animal Medical Center's medical records and included: signalment, presenting signs, pertinent physical examination findings, clinicopathologic and microbiologic findings, imaging results, cystourethroscopy findings, histopathology, and treatment modality implemented. Specific interventions chosen were clinician dependent and details were recorded. Urethral stenosis was determined to be effaced when the lesion either underwent BD or a stent (temporary or permanent) was placed, and visual evidence of luminal patency was documented using contrast fluoroscopy and cystourethroscopy.

2.2.1 | Cystourethroscopy and cystourethrography

Dogs were given antibiotics peri-procedurally (cefazolin 22 mg/kg IV q2h) immediately before, and until completion of cystourethroscopy, when appropriate. If dogs were already being treated with an antibiotic based on previous positive culture and sensitivity or based on a presumptive diagnosis of infection, they were not given additional antibiotics. Antibiotic choice was clinician-dependent. All cystoscopic procedures were performed with the animals in dorsal recumbency under general anesthesia and using sterile technique.

A rigid 30° cystoscope (Karl Storz 2.7 mm, Flanders, New Jersey; Richard Wolf 2.7 mm, Vernon Hills, Illinois) was advanced into the vestibule. The urethra and urinary bladder were evaluated, followed by the vagina and clittoral fossa. If the urethral lumen was too narrow to accommodate the cystoscope, a guidewire was placed into the urinary bladder inside the urethral lumen through the working channel of the cystoscope. The urethra was effaced using BD under fluoroscopic guidance before completing the cystourethroscopy. All lesions were documented (Figure 1) and a sample was obtained using a cup biopsy

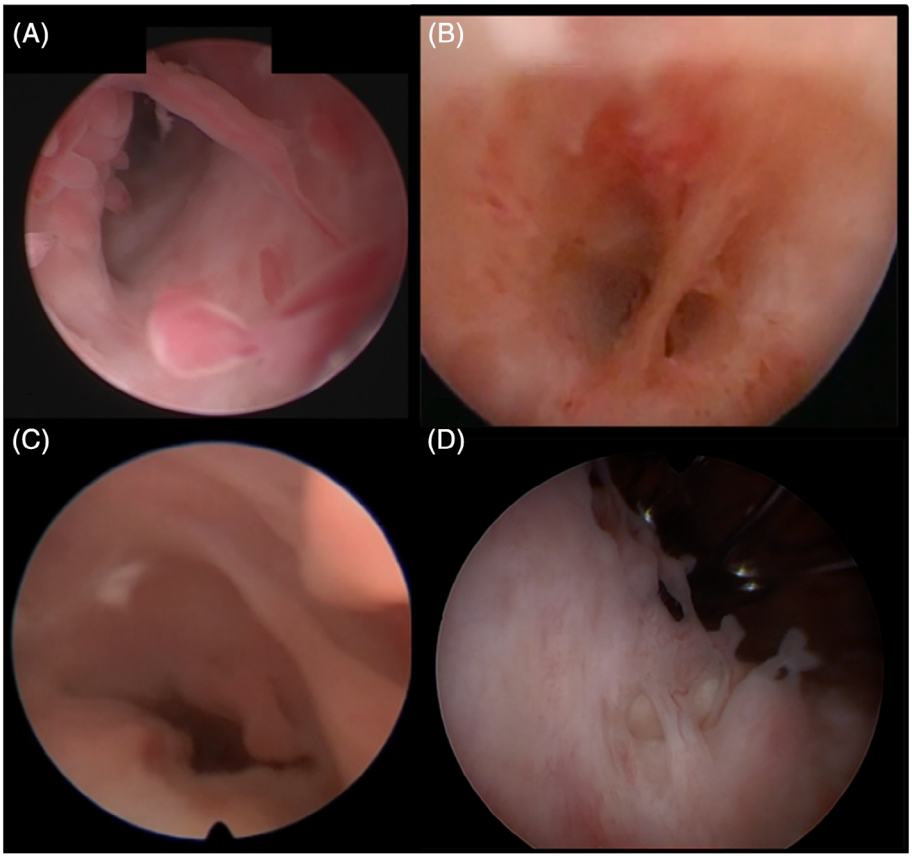

FIGURE 1 Urethroscopic images of 4 different dogs with proliferative urethritis. A-C, Ipsilateral bands of frond-like tissue spanning the urethra and being attached on both ends. These are images of lesions before biopsy or effacement has been performed. D, Frond-like urethral tissue with an SEMS deployed in the background. SEMS, self-expanding metallic stent

instrument through the working channel of the cystoscope for histopathologic evaluation and aerobic culture and sensitivity.

A cystourethrogram was performed in most cases using fluoroscopic guidance to determine the extent and location of the urethral narrowing, as well as to measure the size of the urethral luminal diameter to assist in appropriate sizing of a balloon or urethral stent. To do so, the patient was rotated into lateral recumbency and a sizing catheter (5 Fr sizing catheter, Infiniti Medical, Redwood City, California) was placed in the colon for accurate urethral diameter measurements in order to calibrate and adjust for magnification (Figure 2). The details of this procedure have been described elsewhere.[3,7,9]

2.2.2 | Interventional treatment

Treatment for each dog was clinician-dependent. Procedures included: placement of a cystostomy tube alone (typically percutaneously using a locking loop pigtail catheter, 6 Fr locking loop pigtail catheter, Infiniti Medical LLC, Redwood City, California; Figure 3), debulking the obstructive urethral lesion using a biopsy instrument, fluoroscopic and endoscopic-guided BD of the obstructive lesion (Figure 3), BD and transurethral stenting of the obstructive lesion using a retrievable stent, either metallic (self-expanding Allium Ureteral Stent, Allium Medical, Israel) or latex (Pezzer catheter, Bard Medical, Covington, Georgia), or placement of a permanent self-expanding metallic stent (SEMS; Urethral Stent, Infiniti Medical, Redwood City, California) under fluoroscopic guidance (Figure 3).

2.2.3 | Medical management

Postoperatively, each patient was treated with an immunosuppressive agent, usually in combination with an anti-inflammatory agent. If UTI was documented, appropriate antibiotic treatment was prescribed for a duration of 4 to 6 weeks with serial urine culture recommended to ensure resolution. Urethral relaxants and pain medications were utilized at the discretion of the clinician.

2.3 | Outcome

Re-evaluation typically included urine microbiologic culture and sensitivity, focused urinary tract ultrasound examination or abdominal radiographs, and serum biochemistry (including serum creatinine, blood urea nitrogen, and symmetric dimethylarginine concentrations). When immunosuppressive agents were utilized, CBC and serum biochemistry were performed as necessary to monitor treatment. Frequency and interval of re-evaluation were clinician-dependent. Other data recorded included evidence of persistent lower urinary tract signs, ability to empty the urinary bladder, urinary incontinence, and all clinicopathologic data available from the patients' primary veterinarians during the study period. Follow-up was defined as perioperative (start of medical management with or without effacement to ≤7 days), short-term (8 days to 6 months), and long-term (>6 months). Successful outcome during each time period was determined by the

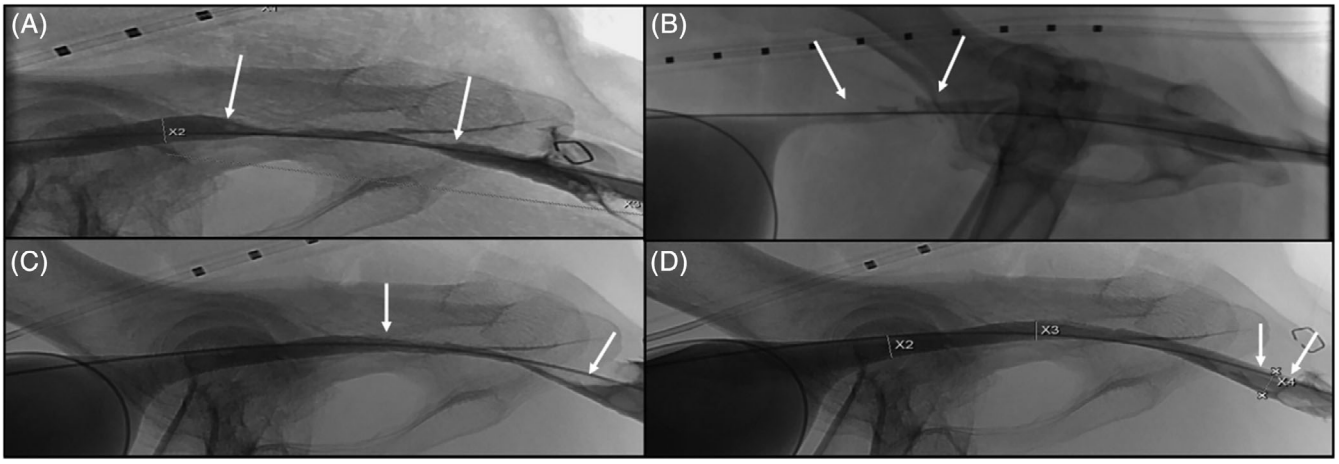

FIGURE 2 Lateral urethral fluoroscopic images of dogs with PU. A sizing catheter is placed in the colon and a guidewire is present in the urethra and coiled in the bladder. A-C, A contrast cystourethrogram was performed to identify the location of the urethral stenosis. The white arrows demarcate the boundaries of the stenosis after the contrast study. D, Measurements taken of a dog postballooning. X2 and X3 (white lines) identify the length of the previous stenosis that is now patent. The white arrows are pointed at X4 (white line), which is being used to measure the diameter of the distal urethra for the appropriate balloon sizing. PU, proliferative urethritis

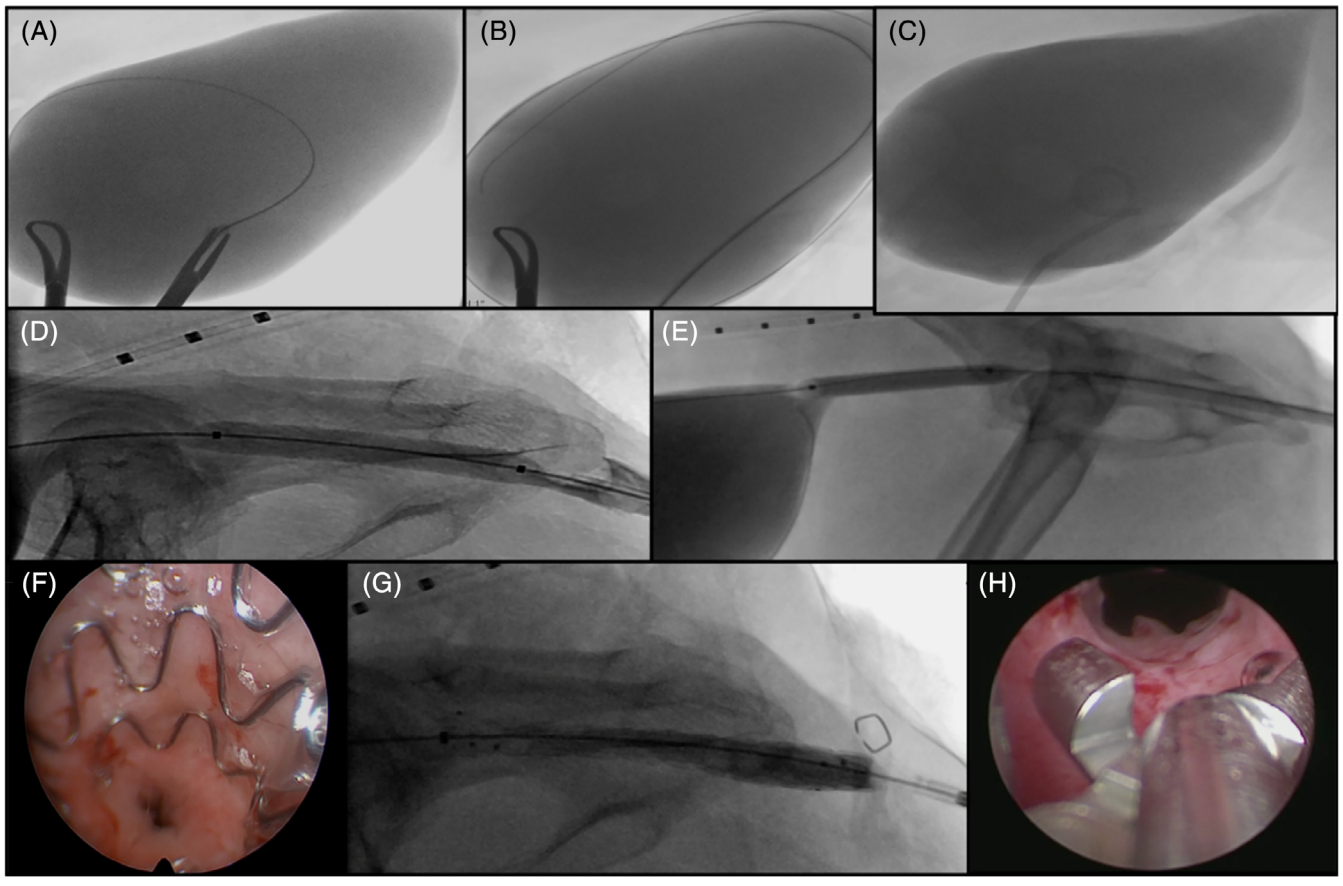

FIGURE 3 Fluoroscopic and cystoscopic images of multiple procedures performed on different dogs. A-C, Fluoroscopic image of a bladder distended with contrast that has been accessed percutaneously with an 18-guage intravenous catheter. A 0.035″ angle tipped hydrophilic guidewire has been inserted through the catheter and looped in the bladder. A locking-loop pigtail catheter (figure C) is placed over the guidewire for use as a percutaneous cystostomy tube. D,E, Fluoroscopic guided balloon dilatation of the urethra using contrast within the balloon to confirm effacement of urethral stenosis. F, Urethroscopic image to confirm successful placement of a silicone covered retrievable stent (RCMS) in a dog with PU. G, Fluoroscopic guided placement of a RCMS in a dog with a long urethral stricture. H, Urethroscopic guided debulking of the lesion without effacement. PU, proliferative urethritis

dog's ability to urinate normally postoperatively while maintaining continued urethral patency. Urethral reobstruction that occurred within 6 months after the first intervention was considered a short-term failure, and after 6 months was considered a long-term failure. Data were recollected from any patient that required additional procedures for recurrent PU with the same outcome criteria. Because 1 dog died in the initial perioperative period and 2 dogs died in the short-term period, data were reported for 11 dogs in the perioperative period, 10 dogs in the short-term period, and 8 dogs in the long-term period.

2.4 | Statistical analysis

Most descriptive statistics are presented as mean and SD. Non-normally distributed data are presented as median and range. Frequency analysis provided frequencies for categorical variables and the percentage contribution to the entire population for that variable.

3 | RESULTS

3.1 | Case selection

Eleven female dogs diagnosed with PU met the inclusion criteria for the study. Breeds identified included Shih Tzu (2), Pug (2), Pitbull Mix (2), Corgi (1), Chow chow (1), Labrador retriever (1), German Shepherd (1), and Rottweiler (1). The dogs ranged in age from 5 to 12 years (median, 8) and all were spayed females. All dogs were evaluated at The Animal Medical Center for UO. One dog had a presumptive obstruction secondary to cystolithiasis. Initial clinical signs noted in the patients' medical records included stranguria (10), pollakiuria (8), and hematuria (3). Ten of the dogs presented with complete obstruction (ie, turgid, nonexpressible bladder, or persistent attempts to urinate without urine production or both) and 1 with a partial obstruction. The latter dog had a history of clinical signs for several months with associated bladder atony, the bladder was difficult to express and the dog dribbled urine with a full bladder. Pertinent physical examination findings were distended urinary bladder (11), thickened urethra on rectal examination (7), and painful abdomen (2).

3.2 | Medical record review

Hematologic abnormalities were uncommon. One dog had neutrophilia (23 780/μL; reference range, 4.9×10^3/μL to 17.6×10^3/μL) with a left shift (bands 1450/μL) and monocytosis (2030/μL; reference range, 0.13×10^3/μL to 1.15×10^3/μL) and another had mature neutrophilia (19.43 x10^3/μL). No dogs were azotemic at initial presentation. Urinalysis was available in 10 dogs, with hematuria in 7 (range, 0-2 per high power field [hpf] to too numerous to count [TNTC]; median, 15-20/hpf), pyruria in 7 (range, 0-2/hpf to TNTC; median 6-10/hpf), bacteriuria in 3 (range, 9-40/hpf to TNTC; median, >40/hpf), and low urine specific gravity in 9 (range, 1.015-1.032; median, 1.021). Six of 10 dogs evaluated were proteinuric on urinalysis, but all of them also had active sediment.

Eight of 11 (72.7%) dogs had a previous history of being treated for UTI. All 11 dogs had urine culture or tissue culture performed before or at the time of urethral biopsy. Seven dogs were receiving antibiotics at the time of the urine culture. Seven dogs had negative urine cultures (5 of 7 while on antibiotics) and 4 were positive; 2 from urine, 1 from calculus (magnesium ammonium phosphate), and 1 from a urethral tissue biopsy specimen (*staphylococcus pseudintermedius* [2], unspecified staphylococcus [1], beta hemolytic streptococcus [1]). Two of 4 dogs with positive cultures were receiving antibiotics. The dog with a positive tissue culture had a negative urine culture 10 days prior and was not on antibiotics. Urine pH was available for 3 of 4 dogs with positive cultures and was alkaline in 2, 1 of each positive for *Staphylococcus* or *Streptococcus* spp. infection, including the dog with a struvite cystolith, which had a urine pH of 7.5 and a *S pseudintermedius* infection. The urine pH of the other dogs in the study without positive cultures on presentation ranged from 6.5 to 7.

Of the 3 dogs with cystolithiasis, 1 calculus was removed (magnesium ammonium phosphate) and the others were not because of their very small size (<1 mm) and the primary clinician's focus on the obstructive urethral lesion. These small calculi were only noted on cystoscopy, and not visible on radiographs. They were considered urinary bladder sediment on ultrasound examination and not analyzed. These 3 dogs did not have a previous history of cystolithiasis. Crystalluria was not present on urinalysis in the 2 dogs that did not undergo calculus removal. The dogs in our study without calculi on presentation did not have a history of cystolithiasis.

Five dogs had ultrasound examination results available for review, 4 had a thickened urethral wall ranging from 1 to 8 mm with concurrent cystitis, and 1 did not have thickening but a severely distended bladder.

3.2.1 | Cystourethroscopy and cystourethrography

All 11 dogs underwent general anesthesia for cystourethroscopy to identify the cause of the obstruction and obtain a biopsy specimen. Nine of 11 had parallel, ipsilateral bands of pale fibrous tissue protruding into the urethral lumen creating obstruction. Seven of 11 had bands of tissue present in the vestibule at the urethral orifice. Five had abnormalities detected in the bladder including a large distended bladder (n = 1), focal areas of polypoid-like tissue throughout the bladder (n = 1), a fibrous band of tissue near the trigone (n = 1), irregular and erythematous bladder mucosa (n = 1), and a large, flaccid bladder with diffuse, erythematous raised lesions throughout the bladder mucosa (n = 1). Urethral stenosis with pale discoloration and circumferential narrowing was noted in 10 of 11 urethral images examined and suspected in 1 from the report. Two dogs had stenosis in the proximal urethra, 4 distally, and 5 described as either multifocal or diffuse throughout the urethra. The 1 dog that did not have a stricture described in the endoscopy report did have smoothly marginated

tissue protruding into the distal third of the urethral lumen, suggesting narrowing. This dog had complete obstruction on presentation.

3.2.2 | Interventional treatment

After the region of stenosis was identified, several different treatments were attempted to achieve urethral patency based on clinician preference. Eight of 11 dogs had lesion effacement performed using fluoroscopic and endoscopic guidance. This was done by urethral BD (6), placement of a SEMS (1), and BD followed by placement of a retrievable covered metallic stent (RCMS; 1). One of the dogs that had BD alone also had a percutaneous cystostomy tube placed during the same anesthetic event. The additional 3 dogs that did not undergo effacement had medical management alone after biopsy of the lesion. Two of these dogs had a cystostomy tube placed under the anesthesia for cystourethroscopy. One of these 3 dogs had some of the proliferative lesions debulked using a biopsy instrument, but the stricture was not effaced. Both dogs with cystostomy tubes had complications associated with the tube; 1 developed uroabdomen after tube placement and the other dislodged the tube 12 days after placement, prompting immediate replacement.

Histopathology

Histopathology was re-evaluated in each case for a definitive diagnosis of PU. Four of 11 (36%) dogs had histopathology consistent with lymphoplasmacytic and neutrophilic urethritis, 4 had a mixture of either lymphoplasmacytic, eosinophilic, neutrophilic, or histiocytic urethritis, 1 (9%) lymphoplasmacytic urethritis, 1 neutrophilic urethritis, and 1 eosinophilic and neutrophilic urethritis. Nine of 11 (82%) had evidence of lymphoplasmacytic cellular infiltrates and 9 of 11 had evidence of some neutrophilic infiltration.

Postprocedure management

The median hospitalization time postprocedure was 48 hours (mean, 73.2 hours; range, 12-216 hours). All dogs received medical management for PU after their procedure. Nine of 11 dogs were treated with antibiotics; 8 with amoxicillin/clavulanic acid (10.6-15.6 mg/kg PO q12h; Clavamox, Zoetis Services LLC, Parsippany, New Jersey) and 1 with enrofloxacin (9.7 mg/kg PO q24h; Baytril, Bayer, Leverkusen, Germany).

Nine of 11 dogs received azathioprine (1.5-2.5 mg/kg PO q24h for 2 weeks and then q48h thereafter; Imuran, Prometheus Laboratories Inc, San Diego, California) as part of their treatment plan, either in combination with prednisone in 7 of 9 (starting dose of 0.9-2.37 mg/kg PO q24h and then tapered over a period of 3-4 weeks), or in combination with piroxicam in 2 of 9 (0.3-0.33 mg/kg PO q24h; Feldene; Pfizer Inc, New York, New York). One dog was treated with chlorambucil (5.43 mg/m^2 PO q24h) and prednisone, and 1 with mycophenolate (8.28 mg/kg PO q12h; Cellcept, Genentech, San Francisco, California) alone. Three of the 9 dogs treated with azathioprine did not respond in the short term, but 2 of these 3 dogs did not undergo lesion effacement. One dog that had lesion effacement (BD and RCMS) and did not receive azathioprine responded in the short term, and remained free of obstruction for >6 months. Medication prescribed for urethral relaxation and pain management included tamsulosin (0.009-0.024 mg/kg PO q12-q24h; Flomax, Astellas Pharma Inc, Tokyo, Japan), prazosin (1-2 mg per dog PO q8-12h; Minipress, Pfizer), tramadol (4.3-5 mg/kg PO q8h; Ultram, Ortho-McNeil-Janssen Pharmaceuticals, Inc, Titusville, New Jersey), and codeine (1.1 mg/kg PO q8h; generic).

Outcome

Eleven dogs had data available in the perioperative period (≤7 days), and 10 of 11 survived to hospital discharge. One dog was euthanized 4 days after effacement because of bladder atony, but the urethra was patent at the time of euthanasia. Ten dogs were followed over the short term (8 days to 6 months from diagnosis) and 8 dogs had data available over the long term (>6 months after diagnosis). Nineteen procedures performed in 11 dogs because of recurrence of UO either once (n = 5) or twice (n = 3). Two additional instances of UO recurrence were documented, but these dogs were euthanized at the time of reobstruction and another procedure was not elected at 164 days and 196 days, respectively.

At the time of the first procedure, 8 of 11 dogs had the lesion effaced either by BD alone (n = 6) or stent placement (n = 2; SEMS or RCMS). The 3 dogs that did not undergo lesion effacement at the first procedure experienced short-term reobstruction at a median of 101 days (range, 22-164 days), requiring another procedure. Of the 8 dogs that had effacement performed, all had a patent urethra after the procedure, and 1 was euthanized for bladder atony 4 days later.

All 7 dogs that had effacement performed and were discharged from the hospital had urethral patency documented over the long term, or to the time of last follow-up. One was euthanized for hyperadrenocorticism at 158 days, but was urinating normally since the first procedure. The dog with RCMS placement had urethral patency for >6 months, but re-presented at 196 days with recurrence of UO. This dog was euthanized because of financial constraints, and urinalysis was not performed to determine if reinfection had occurred.

3.2.3 | Follow-up

Seven of 9 (78%) dogs that had urine available for analysis during the follow-up period were documented to have recurrent UTI after their initial diagnosis. Three of 7 (43%) had mixed bacterial infections with the most common bacterial isolate being enterococcus in 5 of 7 (71%). Six of 7 had urine available for evaluation at the time of reobstruction and 4 of 6 (67%) had evidence of UTI.

Five of 10 (50%) dogs in the short term were documented to have incontinence after their diagnosis. Four of 5 experienced incontinence after stent placement (1 permanent metallic stent and 3 temporary stents), and 1 unrelated to a stent. Of the 6 dogs that had stents placed in our study, 4 (67%) developed urinary incontinence. Incontinence resolved once the temporary stents were removed in 2 of the 3 with stents, whereas 1 required treatment

with phenylpropanolamine for resolution, even after the stent was removed. The dog with the permanent stent had incontinence at the time of last re-evaluation (158 days after effacement) before it was euthanized. Four of the 5 (80%) dogs with short-term incontinence also had recurrent UTI.

3.2.4 | Recurrence

Seven of 10 dogs (70%) had at least 1 documented recurrence characterized by the inability to urinate. All 3 dogs (100%) that did not have lesion effacement at the initial procedure had recurrence at a median of 101 days. In comparison, the 4 dogs that had effacement performed experienced recurrence at a median of 687 days (range, 196-1738 days) after the first procedure. Two dogs were euthanized because of reobstruction at 165 days and 201 days, respectively.

All 5 dogs that had a second procedure performed for reobstruction underwent effacement using BD (3) or BD with RCMS (2). Two of 5 procedures (1 BD and 1 RCMS) were immediately successful and the dogs achieved long-term urethral patency. Three additional failures occurred in those that had BD alone performed (2), at 2 days and 6 days after BD, respectively, and 1 at 21 days after a RCMS was placed. The 2 dogs that failed BD had evidence of fibrinous tissue occluding the urethral lumen immediately after BD, and a temporary retrievable stent subsequently was placed, which resolved the obstruction. One of these dogs had a temporary Pezzer catheter placed across the entire urethra and sutured into the vestibule after BD failed. The catheter remained in place for 63 days and resulted in long-term urethral patency for an additional 1072 days. The other dog had a RCMS placed 6 days after BD, resulting in a patent urethra. This dog was euthanized 3 days later after development of septic cellulitis of the hind limb associated with the same organism cultured from the urine. The 1 RCMS failure was caused by kinking of the stent (Figure 4) which was easily resolved by passage of an 8 French red rubber catheter through the stent lumen. After 2 weeks, the dog was urinating normally and the RCMS was removed. The dog continued to urinate normally over the long term (>926 days).

When all procedures were evaluated, the median time to recurrence, or last follow-up, was longest for dogs that had a stent placed, either temporary or permanent, with recurrence occurring at a median of 101 days with no effacement (range, 22-164 days), 452 days with BD alone (range, 2-1738 days), and 843 days if any type of stent was placed (range, 158-1072 days).

Overall, 19 procedures were performed in 11 dogs because of recurrence of UO. Five dogs had repeated procedures performed (2 had 2 procedures and 3 had 3 procedures). The overall long-term follow-up time for urethral patency of PU for all 4 dogs that survived perioperatively and had multiple procedures performed when obstruction was documented was a median of 952 days (range, 843-1072) and none of these patients died or were euthanized because of UO associated with PU.

At the time of last follow-up, 4 of the 10 (36%) dogs were still alive and 1 was lost to follow-up at 6 months. Of the 5 dogs that were dead, 2 were euthanized because of complications related to PU after reobstruction, 2 were euthanized because of complications secondary to UTI; 1 had necrotizing fasciitis, and the other dog was euthanized because of disseminated Acremonium infection suspected to be secondary to immunosuppression from cyclosporine. The median follow-up time from diagnosis to last follow-up for the 10 dogs that survived after their first procedure was 749 days (range, 158-2000 days).

4 | DISCUSSION

Proliferative urethritis affected only female dogs and was associated with complete or partial obstruction. Most affected dogs had a history of UTI (73%), which is consistent with the previous literature.[1-4] Effacement of the urethral stenosis, either by BD or stent placement, effectively achieved long-term successful outcome for these dogs. Proliferative urethritis is a recurrent disease with 70% (7/10) of dogs in our study having disease recurrence, and reobstruction was the most common cause for euthanasia (n = 2). Stent placement seems to provide a longer duration of urethral patency than BD alone.

Urinalysis showed that the majority of affected dogs had pyuria and hematuria, consistent with other studies.[1,2] Most dogs had a

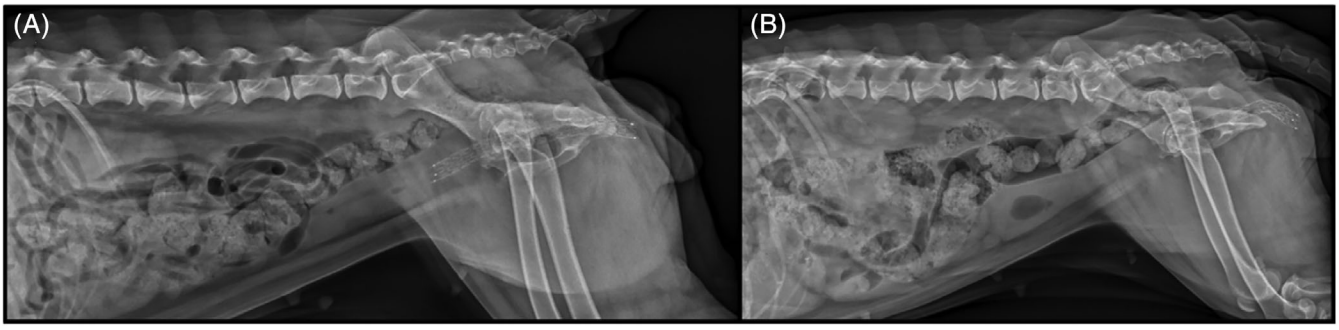

FIGURE 4 Lateral abdominal radiographs after placement of a RCMS in a dog with PU. A, Successfully placed RCMS, effacing the urethral stenosis and achieving urethral patency. B, Radiographs taken in the same dog 21 days later when it presented for a recurrent UO. The stent is kinked in the distal urethra. The obstruction was resolved after placement of a temporary red rubber urinary catheter through the vestibule. PU, proliferative urethritis; RCMS, retrievable covered metallic stent; UO, urethral obstruction

history of a UTI (8/11, 73%). Previous studies have indicated that the inflammatory component of PU is associated with UTI.[1-4] Only 4 dogs had positive cultures at the time of diagnosis, but 5 of the dogs with negative cultures were receiving antibiotics at the time of sample collection. In a recent study, FISH analysis was evaluated in dogs with PU, and it was noted that urethral tissue was positive in 7 of 13 (54%) dogs for adherent or invasive bacteria or both, and 5 of those dogs were receiving antibiotics at the time of diagnosis. Three of the dogs in the previous study that were FISH positive had negative aerobic bacterial urine cultures.[4] These results suggest that some dogs with bacterial colonization of the urinary tract may not be identified by aerobic urinary cultures. Additional testing by FISH analysis or empirical treatment for complex UTI should be considered.

Only 3 dogs in our study had cystoliths on presentation. One of these dogs was presumed to be obstructed secondary to a struvite cystolith that was removed by cystotomy before PU was diagnosed. This dog immediately became obstructed after cystotomy, and PU was diagnosed by cystourethroscopy as the cause of obstruction. The lesion in this dog was diffuse and obstructive throughout the entire urethra. Two other dogs had small cystoliths at the time of diagnosis that were not removed during cystourethroscopy.

Our cystoscopic findings were consistent with those of previous studies.[1,4] Pale, ipsilateral bands of tissue protruded into the urethral lumen in 9 of 11 (82%) dogs. These bands typically were anchored on 2 ends, both of which were on the same side of the urethral lumen (Figure 1). Seven of 11 dogs (64%) also had bands of tissue present within the vestibule, which was noted in 8 of 13 dogs in a previous study.[4] With the aid of cystourethrography, urethral stenosis or narrowing was documented in all 11 dogs of our study, which has not been reported previously. Given the consistent cystourethroscopic appearance of PU, if ipsilateral bands of tissue are seen with urethral narrowing on urethroscopic examination, the clinician should consider a diagnosis of PU, rather than transitional cell carcinoma (TCC), until histopathology is available. In our experience, TCC has a different cystoscopic appearance, causing a mass lesion that is vascular, proliferative, often mineralized, and more irregular and disorganized in appearance.

Most dogs in our study had lymphoplasmacytic infiltrates on histopathology (82%), which is consistent with previous studies.[1,4] Two dogs had monocellular infiltrates, whereas the others had a mixed population of inflammatory cells. In a previous study,[4] the presence of invasive and adherent bacteria on FISH did not correlate with the type of inflammation in the urethra, indicating that urethral inflammation is nonspecific.

Of the 7 dogs that underwent lesion effacement in their first procedure, 6 (86%) had urethral patency for >6 months, and 1 was euthanized after 158 days for reasons related to hyperadrenocorticism. All 3 dogs that did not undergo effacement at the time of diagnosis had recurrent UO within the short term. Whether dogs underwent BD, BD and stenting, or stenting alone, all methods of effacement were more successful for maintaining patency than no effacement or medical management alone.

In our report, all 7 dogs that survived the perioperative period after urethral effacement could urinate normally after the procedure. A cystostomy tube was placed in 3 dogs for urinary diversion. One dog with concurrent UTI had effacement performed (BD) and a cystostomy tube placed temporarily until an effective antibiotic was started, allowing return of normal urination approximately 1 week later. One dog that did not have a cystostomy tube placed was euthanized for bladder atony 4 days after BD. This dog could urinate, but could not empty its bladder completely. A cystostomy tube potentially could have allowed more time for return of bladder function. A cystostomy tube also can be considered when urethral effacement cannot be performed. Caution must be taken because of the high rate of UTI, and risk of uroabdomen.

Most dogs (78%) in our study had recurrent UTI after initial diagnosis. Furthermore, 4 of 6 dogs (67%) had UTI at the time of reobstruction. As described in previous studies,[1,2,4] infection likely plays an important role in PU, but we cannot definitively conclude that bacteria are the sole cause for the development of the obstructive lesions in the urethra. The rationale of medical management is to treat underlying UTI while providing immunosuppression to decrease urethral inflammation and prevent further tissue proliferation. Routine follow-up including urine cultures every 3 months was recommend in all patients, but unfortunately poor compliance was encountered. Along with antibiotics, treatment using a tapering course of immunosuppressive drugs (eg, corticosteroids, azathioprine) is recommended. Most dogs were treated with azathioprine, but prospective studies are needed to determine the efficacy of such treatments. It is unclear if effacement and antibiotics alone are sufficient without need for immunosuppressive drugs.

Recurrence of UO was common, with 7 of 10 (70%) dogs developing another obstruction during the study period. Three of these dogs never underwent effacement, and obstruction occurred in the short term (median, 101 days), whereas 4 initially were effaced and reobstruction occurred in the long term (median, 687 days).

Overall, all 5 dogs with stents experienced urethral patency over the long term (median, 843 days) compared with those that underwent BD alone (median, 452 days) or no effacement (median, 101 days). Urethral stents previously have been used successfully in 2 dogs with PU.[7,8] Given the potential of treatment failure with BD or medical management without effacement, it may be necessary to place a temporary urethral stent in dogs with documented stenosis to maintain urethral patency long term. Although the number of cases was small, both SEMS and RCMS were effective in our study. The SEMS was chosen in 1 case before availability of RCMS. The benefit of SEMS is that it avoids the need for repeat stenting because most PU lesions involve the entire, or the majority of the urethra. Urinary incontinence may occur if the stent must remain in place, as compared with with TCC[10] or focal urethral strictures.[7]

Of the dogs that had a urethral stent placed (SEMS or RCMS), 4 of 6 (67%) developed urinary incontinence. The 1 dog that had an SEMS placed was incontinent at last follow-up and, of the 3 dogs with temporary RCMS placement, 2 had resolution of incontinence after stent removal. The 1 dog with continued incontinence was managed successfully using phenylpropanolamine. The 67% incontinence rate in our study contrasts with a previous study on the stenting of benign UOs, where 2 of 8 dogs without a history of urethral sphincter mechanism incompetence developed urinary incontinence.[7] Only 1 dog in the previous study had PU, and thus incontinence after stenting in

dogs with PU may be of more clinical relevance than in dogs with other benign UOs.

Our study had several limitations, the most important being the small number of cases in each treatment group, its retrospective nature, the number of different treatments employed, failure of client compliance for UTI management and follow-up, and variable long-term medical management. These limitations precluded adequate statistical comparisons. Prospectively evaluating different immunosuppressive regimens with a standard effacement procedure could help answer remaining questions.

In conclusion, we further characterized PU as a recurrent disease of the urethra in female dogs. It has a distinct cystoscopic appearance and is most commonly associated with urethral inflammation, UO arising from urethral stenosis, and UTI. When comparing medical management alone to lesion effacement, effacement seemed to be more effective at achieving ureteral patency. Balloon dilatation and urethral stenting both were safe ways to efface stenotic lesions, but urethral stenting seemed to achieve better long-term outcome.

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CONFLICT OF INTEREST DECLARATION

Allyson Berent and Chick Weisse are consultants for Infiniti Medical, LLC.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Authors declare no IACUC or other approval was needed.

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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