

CASE REPORT

Companion or pet animals

Effective treatment of late-onset urinary incontinence with a slow-release GnRH analogue implant in an entire male dog with bilateral ectopic ureters

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Abstract

A 2-year-old, mixed breed dog of predominantly labrador retriever genotype and phenotype, entire male presented with a 6-month history of urinary incontinence. The dog had a continuous urine dripping without straining. The urine bladder was small. No neurological abnormalities were found. Haematology, biochemistry, urinalysis and plain abdominal radiographs, including the urethra, were without remarkable findings. On abdominal ultrasonography, caudally displaced ureters were detected. Contrast-enhanced computed tomography subsequently confirmed bilateral ectopic ureters entering the prostatic urethra. As the dog had remained urinary continent until the onset of sexual maturity, it was hypothesised that the dog would regain continence if it returned to a sexually inactive state. A slow-release gonadotropin-releasing hormone analogue (deslorelin) implant was administered subcutaneously in the neck. The incontinence started to decrease after 4 weeks, and the dog was completely continent after 6–7 weeks. Continence was maintained with repeat dosing of gonadotropin-releasing hormone implants.

BACKGROUND

Ectopic ureters (EU) in male dogs are, when diagnosed, often associated with severe urinary incontinence (UI).¹ To achieve continence, open surgery or cystoscopy-guided laser ablation is needed.^{2,3} Cystoscopy-guided laser ablation is less invasive than open surgery, but can only be applied on intramural EU and requires both endoscopic and laser equipment.² Both techniques require an experienced surgeon.

The present case was a mixed breed dog of predominantly labrador retriever genotype and phenotype, entire male with severe UI starting at 1.5 years of age. Bilateral EU openings at the prostatic urethra were diagnosed. In this dog, UI was successfully reversed with a slow-release deslorelin implant without any additional treatment. In a situation where surgical treatment of EU is not available, contraindicated or cannot be afforded by the owner, treatment with a gonadotropin-releasing hormone (GnRH) analogue may be an alternative to control UI.

CASE PRESENTATION

A 2-year-old, mixed breed dog of predominantly labrador retriever genotype and phenotype, entire, male weighing

35.6 kg was presented with UI that began when the dog was around 1.5 years old. The owner correlated the onset of UI to the onset of sexual maturity in the dog. The UI was severe. The owner described the dog as having a continuous dripping of urine when it was awake and walking around. No straining behaviour had been observed. The ventrum surrounding the prepuce was continuously wet from urine, giving the dog a constant, strong urine smell regardless of cleaning. The urinary leakage was more pronounced when the dog was relaxed and asleep, resulting in large urinary pools on the surfaces. The dog's UI was previously treated with phenylpropanolamine (Propaline vet, Vetoquinol, 1.4 mg/kg every 8–12 hours per os [orally]), estriol (Incurin, MSD Animal Health Sweden, 1 mg every 24 hours per os) and oral amoxicillin (Amoxival vet, Ceva Animal Health, 8.5 mg/kg every 12 hours per os), with no improvement noted. The dog received no medication at the time of presentation. In addition, the owner thought the dog had been drinking and urinating larger volumes than expected from a young age. The estimated daily water intake at the presentation was approximately 2 L (56 mL/kg). After swimming, the dog had had two incidents of cold-water-tail (acute caudal myopathy). There was no history of trauma.

On physical examination, the dog had a strong smell of urine, a wet ventrum and a constant dripping of urine. No

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straining behaviour was observed in the examination room. The urinary bladder was small and soft. No manual expression was attempted. There were no signs of neurological deficits. Specifically, the placing reaction of the hind legs, the bulbourethral and anal reflexes were normal. Physical examination was otherwise unremarkable, except for a concurrent bilateral otitis externa with *Malassezia*.

INVESTIGATIONS

Initial bloodwork and urinalysis were performed to find signs of inflammatory processes and organ failure that could contribute to the potential polyuria/polydipsia, for example, urinary tract infection or renal insufficiency. The haematology was unremarkable besides a mild left shift (band neutrophils were 1.0 G/L, reference range: 0.0–0.30 G/L), probably explained by the concurrent external otitis. Biochemical analysis was normal, including renal and liver parameters, total protein and albumin, C-reactive protein and electrolytes. Urinalysis revealed hyposthenuria with a specific gravity (USG) of 1.007 and the presence of amorphous crystals in the sediment. The subsequent bile acid stimulation test was normal. Therefore, portosystemic shunting was considered a less likely cause of the potential polyuria/polydipsia and amorphous urinary crystals. Due to the hyposthenuria in the initial urinalysis, the owner was asked to collect urine every other hour for 1 day. The USG in the collected samples varied between 1.015 and 1.027, making a central diabetes insipidus unlikely. Polyuria was considered a less likely primary cause of the UI, although a decreased concentrating ability was not excluded.

Diagnostic imaging procedures were performed by European College of Veterinary Diagnostic Imaging residents under specialist supervision. Plain abdominal radiographs, including the urethra, were normal. On abdominal ultrasonography, bilateral urinary jets were identified with colour Doppler in the most caudal part of the urinary bladder neck, 5–7 mm cranially to the prostate (measuring $4.7 \times 2.9 \times 4.1$ cm) (Figure 1). The rest of the abdomen was unremarkable. On four-dimensional computed tomography excretory urography, both ureters joined the caudal part of the urinary bladder trigone. From each ureterovesical junction, a thin intramural course of contrast medium was identified in a caudomedial direction abutting the prostatic urethra. Moreover, the early presence of contrast medium was identified in the prostatic urethra (Figure 2). Therefore, intramural EU opening in the prostatic urethra was suspected.

TREATMENT

The initial plan was to proceed to surgical correction of the EU. As the UI had begun when the dog started sexual activity, it was hypothesised that it would regain continence if it returned to a sexually inactive state. The major hypothesis at the time was that the normal growth of the prostate tissue at puberty had negatively influenced the urodynamics of the caudally displaced ureters. After discussion with a specialist surgeon, it was concluded that reducing the prostatic volume and a reduction of the prostate tissue would not adversely affect subsequent neoureterostomy if castration did not alle-

LEARNING POINTS/TAKE-HOME MESSAGES

- Developmental abnormalities in the urinary tract cannot be ruled out even if urinary incontinence starts later in life.
- The reported median age of onset of urinary incontinence in male dogs with ectopic ureters is 4.5 months.
- Male dogs have a better prognosis for continence after surgical treatment than female dogs.
- Consider minimal-invasive treatment options, such as cystoscopy laser ablation, for the treatment of urinary incontinence associated with intramural ectopic ureters.

viate the UI. The treatment options were then discussed with the owner. Surgery was offered as a first option as it is the standard of care. Second, the owner was informed of the hypothesis of restoring urinary continence with prostate size reduction. As castration can be associated with UI, chemical castration was recommended instead of surgical neutering. The owner chose to try treatment with a slow-release GnRH analogue implant. With the owner's consent, a 4.7 mg deslorelin implant (Suprelorin, Virbac) was administered subcutaneously in the neck region. The dog received no other medication to control UI.

OUTCOME AND FOLLOW-UP

Contact with owner was kept through email correspondence. The owner reported that there was no change in the dog's UI until 4 weeks after administration of the GnRH implant. Starting then, the amount of leaked urine decreased until the dog became completely continent 6–7 weeks after the admin-

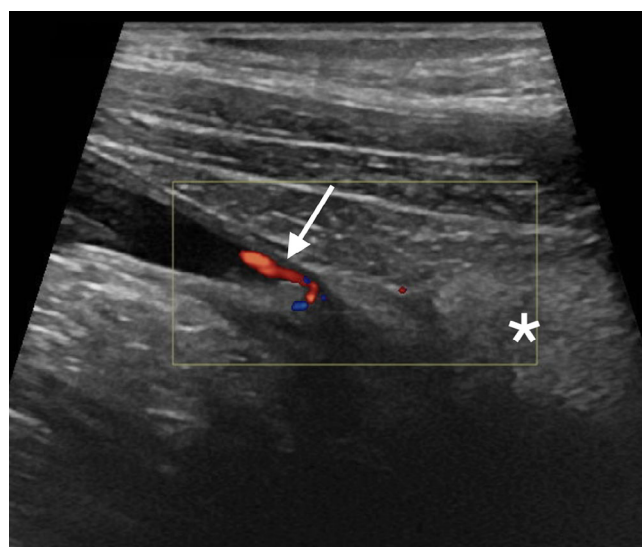


FIGURE 1 Sagittal ultrasound image of the urinary bladder showing caudal location of the ureteral jet with colour Doppler (white arrow). The prostate is located immediately caudal to the jet (white asterisk). The patient was in dorsal recumbency using a Logic E9 ultrasound machine with a 11 MHz linear probe (General Electric).

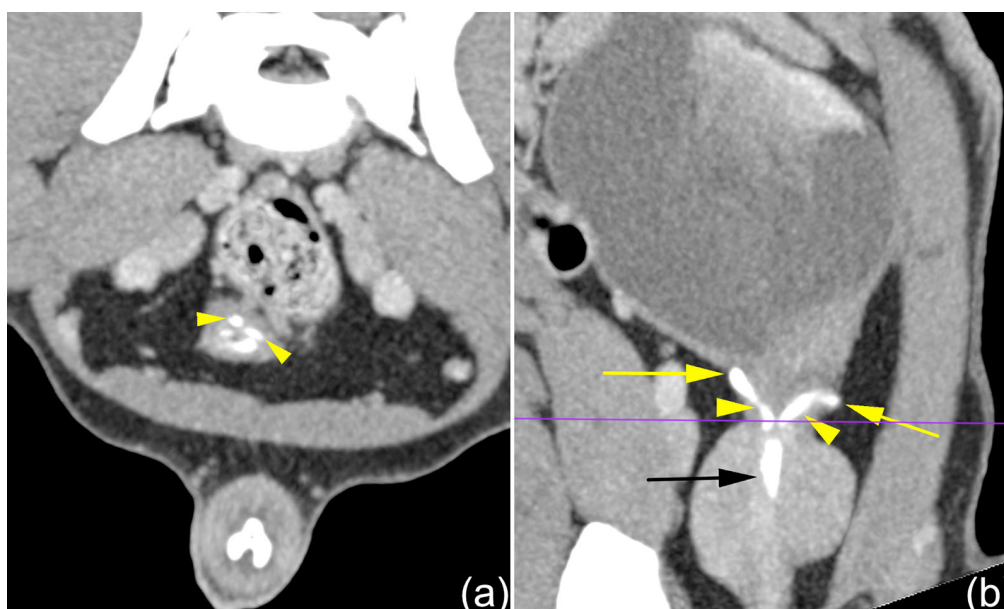


FIGURE 2 Transverse (a) and dorsal (b) plane reconstructions of the four-dimensional computed tomography excretory urography showing caudal location of the ureterovesical junctions (yellow arrows) in the urinary bladder trigone and bilateral caudal intramural course (yellow arrowheads) abutting the prostate. Early leakage of contrast medium through the prostatic urethra (black arrow) is also noted. The location of the transverse reconstruction is represented by a purple line on the dorsal reconstruction.

istration of the GnRH implant. The dog remained urinary continent at follow-up 5 months after the implant. Subsequent follow-ups were performed at the local veterinarian. A second deslorelin implant (9.4 mg) was then administered 8 months after the first. Six months after the second GnRH implant, the dog developed signs of UI. Urinalysis showed haematuria, pyuria and the presence of rod-formed bacteria. The urinary culture was positive for non-haemolyzing *Escherichia coli* bacteria. The dog was first treated with sulfamethoxazole and trimethoprim, which was changed to enrofloxacin (5 mg/kg every 24 hours for 10 days) based on resistance profile. Three days after the end of antibiotic treatment, the dog still presented intermittent UI. Urinalysis was unremarkable and urine culture was negative. Ultrasonography of the lower urinary tract showed moderate thickening of the caudal walls of both ureters, possibly indicating sequelae from altered urine flow due to the EU⁴ or a sign of ureteritis, although no other sign of inflammation could be identified (normal urinary bladder wall and surrounding fat). The prostate was smaller than before, $2.2 \times 1.0 \times 1.8$ cm, with normal echogenicity. Clinically, the dog had shown signs of sexual behaviour (interest in female dogs, sporadic riding of toys). Following treatment, and without additional medication, the UI spontaneously ceased, likely as a secondary effect of resolving the urinary tract infection. The dog received a third deslorelin implant (9.4 mg) 12 months after the second one. The owner had noted a mild UI. There was no sign of urinary tract infection at the time. A fourth 9.4 mg deslorelin implant was administered after another 10 months due to the return of continuous UI comparable to the initial presentation, without the presence of a urinary tract infection. On abdominal ultrasonography, the prostate measured $3.7 \times 1.3 \times 1.7$ cm. The dog regained continence 2 weeks after the administration of the new 9.4 mg deslorelin implant. At the time of writing this report, the dog has been followed for 2.5 years.

DISCUSSION

This case describes the clinical characteristics, diagnosis and medical treatment of an entire male dog with bilateral EU that developed severe UI at 1.5 years of age. No other underlying metabolic or neurological causes nor concurrent developmental abnormalities of the urinary tract were found. Because the UI had started at the onset of sexual maturity, it was hypothesised that continence would be regained if the dog returned to a sexually inactive state. The dog was chemically neutered with a slow-release GnRH analogue (deslorelin) implant, and the dog regained complete continence 6–7 weeks after administration. To the authors' knowledge, this is the first described case of using a GnRH analogue depot to control UI in a male dog with EU. It is a minimally invasive treatment with low morbidity that can easily be administered without the need for expensive equipment and surgical skills. Therefore, a slow-release GnRH analogue implant may be an alternative to control UI in adult male dogs with EU when surgical treatment cannot be provided, is contraindicated or considered unaffordable by the owner.

The signalment and clinical presentation of the presented case is representative of dogs with EU. Labrador retriever is a common breed among dogs diagnosed with EU in the UK, the USA and Europe.^{1,3,5–7} Traditionally, EU has been diagnosed in predominantly female dogs.^{6,8–10} However, EU has gradually been recognised and diagnosed in more male dogs. In a recent study of dogs surgically treated for EU, the proportion of male dogs was 48%.^{3,7} This may be explained by the increased awareness of the different clinical presentations in male dogs compared to female dogs.

The median age of onset of UI in male dogs was 140 days, ranging from 28 days to 4 years, which was significantly higher than reported for female dogs.^{3,6} Thus, the late onset of UI does not rule out the presence of developmental abnormalities such as EU. The reason for the delayed onset of UI

in male dogs with EU is unknown. Holt and Moore suggest that it may be related to the longer urethra in the male dog and that UI developed when urethral tone declines with age.⁶ In contrast, a recent study of entire beagle dogs showed that urethral resistance and integrated pressure increased with puberty.¹¹ Thus, an entire male dog with a normal urinary tract anatomy is expected to have an improved continence after puberty. Still, entire male dogs with EU develop UI at adulthood as was seen in the present case.^{3,12}

The diagnostic methods used to identify EU have evolved over the past decades. In comparison to traditional diagnostic radiography using intravenous urography, different forms of contrast cystography, and fluoroscopy, direct visualisation of the lower urinary tract by cystourethroscopy dramatically improved diagnosis and classification of EU and associated congenital abnormalities in the lower urinary tract.¹³ However, cystourethroscopy does not allow for the evaluation of concurrent abnormalities in the upper urinary tract. With increased availability and improvement of ultrasonographic and computed tomography equipment, procedures and interpretation skills, diagnostic imaging has re-emerged as a useful diagnostic method.^{14,15} Cystoscopy remains the recommended modality to diagnose EU and allows for the direct ablation of intramural EU when present.¹⁵

Ultrasonographic diagnosis of an ectopic ureter includes lack of identification of a ureteral jet in the urinary bladder using colour Doppler, visualisation of the papilla caudal to the bladder neck, or visualisation of a jet of urine caudal to the bladder neck, also using Doppler.¹⁶ Diagnostic imaging detection of intramural EU can be difficult as the EU may normally join the urinary bladder in the trigone area but have an intramural path directly connected to the urethra instead of entering the urinary bladder lumen. Computed tomography is therefore dependent on the right timing of the contrast medium through the intramural path to confidently detect the ectopic characteristic.¹⁷ Using four-dimensional computed tomography excretory urography, allowing temporal reconstructions, therefore enhances the detection of the abnormal contrast medium path and its direct passage to the urethra. This technique, used in this case report, increases the sensitivity of detection from 73% to 97%.¹⁸

Surgical correction of EU is the only treatment that can result in persistent urinary continence. Traditionally, EU surgical correction is performed via open surgery. The elected surgical procedure depends on the location and morphology of the EU and the presence of concurrent pathologies in the urinary tract.^{13,19} If the ureter joins the bladder wall close to a normal anatomical position at the trigone and then runs submucosally in the bladder wall to an opening distal to the normal site (intramural EU, which is the most common form of EU), a neoureterostomy can be performed.^{1,3,7,13,19} If the EU enters and empties caudally to the bladder (extramural EU) or caudal to the normal anatomical site at the trigone, ureteral reimplantation is performed.^{1,3,13} If there are unilateral concurrent developmental abnormalities in the urinary tract, for example, hydroureter or hydronephrosis, the surgeon may elect for a ureteronephrectomy.^{1,3,13}

The most common complication after neoureterostomy, ureteral reimplantation and ureteronephrectomy is the persistence of UI.¹³ The prognosis for complete resolution of UI has varied between studies. The proportion of dogs with

long-term complete continence in more recent publications has varied between 47% and 78%.^{3,7,20} The highest degree of post-operative continence has been reported for surgical correction in male dogs,^{1,20} and male sex has been identified as a positive prognostic factor for continence.³ Additional complications after neoureterostomy include perforation of the ureter, cystitis and reflex dyssynergia.^{7,19} Ureteral reimplantation can result in post-operative hydroureter, hydronephrosis, cystitis, transient stenosis, anastomotic dehiscence and loss of normal ureteric peristalsis.¹⁹ In one study, the rate of major complications after EU surgery in male dogs was 26%.⁷

Cystoscopic-guided laser ablation for EU has been developed and successfully used to treat intramural EU. In experienced hands, the treatment can result in 100% urinary continence in male dogs.¹² As with open surgery, continence rates in female dogs are lower.^{21–24} The technique is minimally invasive, has low complication rates, and can commonly be performed on out-patients.^{2,12,21–24} The availability of the equipment needed and experienced operators is probably the primary limiting factor. In the present case, cystoscopic-guided laser ablation was not available. Thus, open surgery was the only treatment alternative that could be offered at the time of diagnosis.

The main advantages of cystoscopic-guided laser ablation for treating EU are that the method is less expensive, less invasive and has lower morbidity than open surgery.² Similarly, treatment with a slow-release GnRH analogue implant is minimally invasive, has low morbidity and has a lower short-term cost compared to surgical techniques.²⁵ Additionally, it can easily be administered without the need for advanced equipment or surgical skills. The major disadvantage is that the GnRH analogue implant provides neither an immediate nor permanent solution.²⁶

The observed relationship between puberty and the onset of UI in the present case evoked the idea that the dog might regain continence if it was returned to a sexually inactive state. The reversible slow-release GnRH-analogue implant was chosen above an irreversible surgical castration.

The initial hypothesis was that the UI was related to the normal growth of prostate tissue, which adversely affected the abnormally positioned ureters, potentially leading to UI by altering their entry angle to the urethra. The dog had its first veterinary appointment for UI at 1.5 years, corresponding to when the prostate reaches its peak volume.¹¹ However, another explanation for the treatment success with the GnRH implant could be direct effects on receptors for the hypothalamic–pituitary–gonad axis hormones expressed in the urinary tract.^{27–32}

GnRH implants have been used for the treatment of UI after ovariectomy in female dogs.³³ Initially, it was believed that the UI was related to hypersecretion of the gonadotropins, luteinising hormone (LH) and follicle-stimulating hormone (FSH) after the loss of negative feedback on the pituitary gonadotrophs after ovariectomy. However, subsequent studies showed no correlation between serum concentrations of LH and FSH and the presence of UI in ovariectomised female dogs.³⁴ An alternative explanation was then discussed. It was hypothesised that the post-castration UI was related to the direct effects on GnRH receptors in the urinary bladder and/or in the sympathetic nerve system in which GnRH serves as a local co-transmitter that facilitates nerve

transmission in ganglia.^{35,36} Sympathetic innervation of the urinary bladder passes through the caudal mesenteric ganglia and hypogastric nerve. Sympathetic stimulation results in detrusor muscle relaxation and urine filling.³⁷ This theory is supported by the finding of dysregulation of urinary bladder function in ovariectomised rats and the improved function after administration of a GnRH analogue.³⁸

Both LH and FSH receptor mRNA and protein have been demonstrated in the urethra of male dogs.²⁸ Although male dogs had a generally lower degree of LH receptor mRNA and protein expression than female dogs, the proximal urethra was an exception, where the expression of LH receptors was higher in male dogs than in female dogs.²⁸ Later, LH and GnRH receptor mRNA expression has been demonstrated in the urinary bladders of both female and male dogs.^{27,29} In addition, expression of androgen receptors has been demonstrated in the urinary bladder and prostatic urethra in humans, rats and rabbits.^{30–32} Therefore, the actual underlying mechanisms for the late onset of UI in male dogs with EU and the observed return of complete continence after administering a slow-release GnRH analogue implant without concurrent treatments remain to be determined. The expression of the hypothalamic–pituitary–gonadal system's hormone receptors in the urinary tract is complex, and hormone secretion patterns differ between dogs that have undergone gonadectomy compared to those receiving a slow-release GnRH-analogue implant. Therefore, it cannot be concluded that surgical neutering or other medical treatments to reduce prostate size would have resulted in continence in the present dog.

In the presented case, UI decreased 4 weeks after implantation of the GnRH analogue and complete continence was achieved 2–3 weeks later, which is in agreement with the reported times for maximum effects on testicular and prostate sizes and semen quality rather than maximum suppression of serum concentrations of LH and testosterone, which usually occurs after 2 weeks.^{39–41} However, there is considerable individual variation in time to effect.^{26,42} As no hormone measurements were performed in the presented case, the timing of LH and testosterone suppression is unknown.

Deslorelin is a potent GnRH agonist. Slow-release implants were developed for male contraception in dogs. Still, the number of applications in companion animals has gradually expanded to include treatment of asymptomatic benign prostatic hyperplasia and hair cycle arrest, as well as achieve the behavioural changes that a surgical castration would give in male dogs.^{25,43–45} Deslorelin implants have also been used in female dogs, for example, for reproduction control and the treatment of post-spaying UI and spay-induced hair coat changes.^{33,46,47}

Deslorelin implants are considered safe and well tolerated.^{26,42} Common side effects include local swelling at the injection site for the first 14 days and initial behavioural changes during the short so-called 'flare-up phase' of a sudden increase in GnRH-stimulated testosterone secretion before the pituitary gonadotrophs become desensitised to GnRH with a subsequent decline in testosterone concentration.^{26,42} Coat changes, general reduction of activity and weight gain may be seen.^{42,46} In the present case, no side effects related to the implants were reported. However, the UI returned as the effect of the implant was wearing off. Lifelong implant placement will, therefore, be needed to maintain continence

in a dog with EU, which, in the end, may be more costly than surgical intervention. A higher dose mainly results in a longer duration of effect rather than increased suppression of the reproductive system.³⁹ There is a large individual variability in the duration of effects. Thus, the optimal interval for implant renewal depends on the individual patient.^{26,39}

Repeated implant administration is generally well tolerated; long-term use for up to 11 years has been reported.^{46,48} Cases of neoplasia of the urinary tract and ovaries have been described in dogs with long-term use of GnRH analogues.^{45,46} A cause–effect of gonadotropins and neoplasia formation in the dog's urogenital tract has not been established, but it is a potential risk to be aware of.⁴⁶

In conclusion, this is a case description of a male dog with bilateral EU that developed severe UI after reaching sexual maturity. Urinary continence was successfully achieved with a slow-release GnRH analogue (deslorelin) implant. The administration of a slow-release GnRH analogue implant is a treatment alternative to consider in adult male dogs with EU when surgical intervention is not feasible.

AUTHOR CONTRIBUTIONS

Jeanette M. Hanson did the diagnostic work-up, treatment plan, follow-up contact with the owner, and wrote the primary draft of the manuscript. **Elisabeth Ball** performed and interpreted the initial ultrasonography and wrote the manuscript. **Alexis Gombert** performed and interpreted the computed tomography and wrote the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare they have no conflicts of interest.

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ETHICS STATEMENT

The dog in this study was evaluated clinically, investigated and treated as part of normal case work-up; thus, an ethics statement is not applicable.

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IMAGE QUIZ

Transverse (a) and dorsal (b) plane reconstructions of the four-dimensional computed tomography excretory urography centred over the urinary bladder neck. The location of the transverse reconstruction is represented by a purple line on the dorsal reconstruction.

MULTIPLE-CHOICE QUESTION

Where is the contrast medium designated by the yellow arrowheads?

POSSIBLE ANSWERS TO MULTIPLE-CHOICE QUESTION

- A. In the lumen of the urinary bladder
- B. In the wall of the urinary bladder
- C. In the urethra
- D. In the kidneys

CORRECT ANSWER

- B. In the wall of the urinary bladder.

The contrast medium is located in the part of the ureters that goes through the urinary bladder wall. This part should be very short and abut the bladder lumen; however, in this dog, there is a long intramural part, abutting the prostatic urethra with a passage of contrast medium in the urethra (black arrow).