Woody's Manly Problem

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Introduction

The prostate gland is the only accessory sex organ in the dog and is responsible for the production of more than 90% of seminal fluid volume[1]. Under the constant influence of androgens, the canine prostate will continue to grow throughout the life of the intact male. By 9 years of age, this constant growth will lead to the spontaneous disease known as benign prostatic hyperplasia (BPH) in 95% of intact males. While most affected animals will never develop clinical signs, BPH can be the source of pain, constipation, tenesmus, dysuria, and infertility as well as predispose dogs to other prostatic diseases such as prostatitis and formation of prostatic cysts[1,3]. While the pathophysiology of canine BPH is not completely understood, it is well known that formation and function of the prostate gland is dependent on testicular androgens with dihydrotestosterone (DHT) acting as the primary stimulatory agent and 17β-estradiol enhancing DHT receptors in the prostate[2-5]. Diagnosis of this disease is typically made on history, clinical signs, and transabdominal ultrasound; however, other diagnostics, such as cytology and culture of prostatic fluid, abdominal radiographs, and cytology and microbial culture of prostatic tissue, prostatic fluid or fluid from prostatic cysts, should also be considered when working up a suspected case. Definitive diagnosis of BPH requires a histopathologic examination of the prostate from a prostatic biopsy[1,3,4]. Treatment of BPH is aimed at decreasing the concentration of DHT, thereby eliminating the primary factor influencing prostatic growth. Gold standard treatment is surgical castration; however, for those who do not wish to castrate or want to breed the affected animal, medical options such as finasteride, tamoxifen, progestogens, estrogens, and gonadotropin releasing hormone (GnRH) analogs and antagonists are available[1,3,5]. Each treatment modality has its own set of pros and cons which must be evaluated for the best treatment of each individual patient.

History and Presentation

Woody is a 9-year-old intact male Labrador Retriever who presented to Mississippi State College of Veterinary Medicine Community Veterinary Service on May 3, 2019 for hematuria. Woody is an indoor dog that is used for duck hunting and frequently swims in the lake behind their apartment. At the time of presentation, he had a history of heartworm disease and was using monthly Heartgard for prevention of more adult heartworms. On the morning of presentation, drops of blood were seen on the floor at home and frank blood was observed coming from Woody's prepuce. In January 2019, another dog in the house had similar clinical signs which resolved on their own.

On initial presentation, Woody was bright, alert, and responsive. His vital parameters were within normal limits with a heart rate of 116 beats per minute, respiratory rate of 36 breaths per minute, and temperature of 101.5° Fahrenheit. Upon abdominal palpation, no abnormalities were felt and no pain or discomfort was elicited. Blood was observed dripping from the prepuce, but there was no evidence of physical trauma. The prostate was noted to be non-painful and of normal size and symmetry on rectal palpation. The rest of his physical exam was within normal limits. Urine was collected via free-catch for a urinalysis and a blood sample was collected via venipuncture for serum analysis to assess for hemolysis. The urinalysis revealed a urine specific gravity of 1.016 and hematuria. The blood serum was normal with no evidence of hemolysis. Woody was discharged with a 14-day course of Enrofloxacin at 10.5mg/kg to treat for suspected prostatitis.

On May 8, 2019, Woody returned with no improvement of clinical signs. At this time, a complete blood count (CBC), serum chemistry, coagulation profile, brucella serology, and urine culture and sensitivity were performed. The CBC, chemistry, and coagulation profile showed all

values within normal limits, the brucella serology was negative, and the urine culture showed no growth after 48 hours. Abdominal radiographs were performed and showed an enlarged prostate and free abdominal fluid. An abdominal ultrasound revealed a small to moderate amount of anechoic free fluid at the tail of the spleen and just cranial to the urinary bladder as well as a small amount of hyperechoic debris in suspension within the urinary bladder. The prostate was diffusely hyperechoic with multifocal smoothly marginated, ovoid, anechoic and hyperechoic regions which were presumed to be prostatic cysts. Samples of the abdominal free fluid, prostate, and presumed prostatic cysts were collected via fine needle aspirate. Fluid analysis of the free abdominal fluid revealed minimal mixed inflammation. Cytology of the prostatic cyst was inconclusive; however, cytology of the prostate itself revealed aggregates of prostatic epithelial cells, scattered erythrocytes, and cellular debris allowing for a diagnosis of benign prostatic hyperplasia.

Anatomy and Pathophysiology

The prostate gland is an oval to spherical, bilobed structure which encircles the proximal urethra and vas deferens of the male dog and is covered by a fibromuscular capsule[1,3,4]. The right and left lobes are separated by a dorsal and ventral midline sulcus, of which the dorsal can be identified via transrectal digital palpation. Each lobe is further divided into lobules by trabeculae with each lobule being made up of tubuloalveolar glands which produce and secrete the prostatic fluid through a series of ducts into the urethra[1]. The gland is located in the caudal abdomen or pelvic cavity where it has contact with the urinary bladder cranially, rectum dorsally, pubic symphysis ventrally, and abdominal wall laterally. Vascular supply is provided by the prostatic artery which originates from the internal pudendal artery and gives rise to the middle rectal artery. The middle rectal artery further branches and enters the prostate through the

dorsolateral surface. Significant anastomoses between the prostatic vessels and the urethral, cranial rectal, and caudal arteries exist which would complicate any attempted prostatectomy[4]. Venous blood drains into the internal iliac vein via the prostatic and urethral veins while the iliac lymph nodes provide drainage for prostatic lymph. The gland is innervated by the hypogastric and pelvic nerves which supply sympathetic and parasympathetic control, respectively[1,4].

Throughout the life of the intact male dog, the formation and function of the prostate gland is under androgen control, particularly that of testosterone and dihydrotestosterone (DHT)[6]. Testosterone, the primary androgen in circulation, is secreted by the testes under the control of luteinizing hormone (LH), which is produced by the pituitary gland. Once in circulation, testosterone can be converted to either DHT via 5α-reduction or 17β-estradiol via aromatization. DHT can then be reversibly metabolized to a second androgen 3α-androstanediol. In the prostate gland, DHT is responsible for stimulating prostatic development, growth, and secretions while 17β-estradiol increases the number of DHT receptors by an unknown mechanism[2,3]. Dihydrotestosterone serves many of the same functions and binds to the same receptors as testosterone; however, DHT binds to receptors much tighter and for a longer duration than testosterone. In the juvenile, this androgenic stimulation allows the prostate gland to reach its mature size and function; as the animal ages, DHT continues to stimulate growth of the prostate via increasing production and expression of prostate growth factor, eventually causing hyperplasia and hypertrophy of both the epithelial and stromal compartments of the gland, as well as cystic hyperplasia, ultimately causing the condition known as benign prostatic hyperplasia (BPH)[1,3,6].

While DHT is widely recognized as the primary mediator of prostatic growth, the exact mechanism of BPH is still unknown. Interestingly, as the animal ages, prostatic DHT

concentrations remain the same and may even increase despite decreasing serum testosterone concentrations[1,2]. Multiple mechanisms have been proposed to explain the prostatic DHT concentrations. In 1980, Wilson proposed the prostatic accumulation of DHT may be due to a combination of an increase in prostatic DHT receptors under the influence of 17β-estradiol and either a decreased conversion of DHT to 3α-androstanediol or an increased conversion of 3α-androstanediol back to DHT[2]. In 1981, Isaacs and Coffey proposed that the increased prostatic DHT concentrations observed during their study were due to metabolic changes within the prostate which favored the net formation of DHT[7]. More recently in 2018, Banerjee et al. suggested that age related changes to nuclear androgen receptor expression may lead to an altered sensitivity of the prostate to serum androgen, leading to BPH via an imbalance in cell death and cell proliferation[6]. Unfortunately, despite these proposed mechanisms, the true pathogenesis of BPH remains unknown.

Diagnostic Approach

Diagnosis of BPH is usually presumptively made from a thorough history and physical exam findings along with any combination of multiple diagnostic tests, including abdominal radiographs, abdominal ultrasound, prostatic fluid analysis, and cytology of prostatic tissue or cyst contents. Definitive diagnosis of BPH can only be made from histologic analysis of a prostatic biopsy[1,3].

While BPH will occur in more than 95% of intact male dogs by 9 years of age, most will never show clinical signs[1]. Of those dogs in which the disease is more severely progressed, clinical signs are associated with those structures most closely associated with the prostate gland. Most commonly, as the gland enlarges, the rectum becomes compressed leading to ribbon or tapered stool, tenesmus, or constipation. Due to the prostate's function of producing seminal

fluid as well as its communication with the urethra, it is also common for affected animals to present with hematuria, preputial or urethral discharge, hemospermia, and subfertility[1,3,4].

On physical exam, every male dog should have a digital rectal exam performed to evaluate for size, shape, symmetry, and evidence of pain. The normal prostate gland should be smooth and symmetrical in shape and should not elicit any pain when digitally palpated[1]. In some dogs, the prostate may not be palpable transrectally due to its increased weight causing it to have fallen cranially into the abdomen. In these cases, the clinician may push the prostate back into the pelvic canal by gently lifting up on the caudal abdomen with their free hand while transrectally palpating with the other[3].

Abdominal and thoracic radiographs, while providing limited value for diagnosing specific prostatic diseases, should be performed to check for evidence of metastasis in any dog in which there is a concern for prostatic neoplasia[1]. For evaluation of the prostate gland, abdominal radiographs may be used to determine the location of the gland within the abdomen as well as evaluate its size, shape, and contour. When performed, both ventrodorsal (VD) and lateral views should be obtained. On VD, the normal prostate size should not exceed 50% of the width of the pelvic inlet. A prostate which is enlarged more than 90% of the pubic brim-sacral distance is indicative of prostatic abscessation, neoplasia, or prostatic cysts[1]. If desired, contrast radiography may be used to overcome the usual lack of contrast in the caudal abdomen in order to provide a landmark for identifying the prostate by highlighting the urinary bladder. An excretory urogram may be valuable in dogs with grossly enlarged prostates to evaluate ureteral patency, especially if there is a concern of renal compromise. Contrast radiography may also be used to evaluate whether a cystic structure is paraprostatic or located within the gland[1].

Ultrasonography provides another excellent imaging technique to evaluate the prostate gland and surrounding structures. Using this imaging modality, the clinician can visualize the external texture, internal architecture, and any cystic structure within the prostate as well as use it for guidance when performing percutaneous aspiration or biopsy[1]. With the dog in dorsal or lateral recumbency, the length, width, and depth of the prostate can be measured and the echogenic texture and uniformity evaluated. A normal prostate should have a homogenous echodense pattern with the normal hypoechoic urethra located between the two lobes. Any distinct areas of hypoechoic and/or hyperechoic tissue likely indicate pathologic changes, like inflammation, neoplasia, or hyperplasia. Cystic structures tend to present as anechoic areas while prostatic abscesses will present as hypoechoic areas. An enlarged prostate with a uniformly echogenic parenchyma is consistent with BPH[1,3]. The volume of a normal mature dog's prostate can be calculated with the following formula: Volume = (0.867 x Body weight in kg) + (1.885 x age in years) + 15.88.[1,3]

Evaluation of prostatic fluid is highly diagnostic for prostatic disease and can be obtained from either semen collection and fractionation or prostatic massage and aspiration[1,3]. The ejaculate of a dog is usually collected in three fractions after manual stimulation. The first two fractions consist of the pre-sperm fraction, which is clear and usually less than 2 mL, and the sperm-rich fraction, which is cloudy and usually no more than 3-4 mL. The third fraction, released over a period of 5-25 minutes, consists of only prostatic fluid. It should be clear, and the volume can be extremely variable, sometimes exceeding 15 mL[1]. Cytology of the third fraction is specific for the prostate and should yield no more than the occasional red blood cell, white blood cell, or squamous epithelial cell. Caution should be used when evaluating bacterial cultures of the ejaculate due to the presence of normal flora in the distal urinary tract. For this

reason, the bacterial count should be quantified, and the type of bacteria present should be isolated[1]. If, for any reason, an ejaculate cannot be easily obtained, prostatic massage immediately followed by a prostatic wash can be performed to collect samples for cytology and culture[1].

Prostatic tissue and fluid, as well as fluid from cystic lesions, can be collected for cytology and culture via fine-needle aspiration. With the dog sedated and in lateral or dorsal recumbency, transabdominal ultrasound guided aspiration can be performed. To collect the samples, a spinal needle with stylet is used and suction is applied with a syringe[1]. The collected samples can then be evaluated both cytologically and for bacterial growth. Normal prostatic fluid is light yellow and translucent, resembles urine, and is normally minimal in amount; therefore, any fluid collected should be considered abnormal. Comparison to a urine sample can be used to rule out accidental puncture of the prostatic urethra or urinary bladder[1]. Any tissue collected in the needle lumen should be expressed onto a slide, made into an impression smear, and evaluated by a pathologist. Utilizing this method, a diagnosis can be made in approximately 50% of cases[1]. Concerns of seeding the needle tract with bacteria from prostatic abscesses or neoplastic cells are commonly raised when considering aspiration of a diseased prostate; however, there is a lack of evidence of this occurring in either veterinary or human medicine[1,3].

Histological examination of a prostatic biopsy is the gold-standard test for determining prostatic disease. Yielding a diagnosis in approximately 66% of cases, a biopsy is warranted when other less invasive diagnostics have failed to provide a diagnosis, when a case is unresponsive to initial therapy, or when an immediate diagnosis is required for prompt treatment[1]. Biopsy samples may be obtained during exploratory laparotomy or percutaneously via either a transabdominal approach or a perirectal approach. With the dog sedated and local

anesthesia used as needed, the transabdominal approach is performed under ultrasound guidance while, with the perirectal approach, the instrument is guided with simultaneous transrectal palpation[1]. Biopsy samples taken during surgery can be collected with a wedge resection from a prostatic lobe or with a Tru-Cut needle. Biopsy samples should always be submitted for histopathology[1]. Complications associated with prostatic biopsies include hematuria secondary to urethral injury and hemorrhage, peritonitis secondary to seeding of bacteria from abscesses, or seeding of neoplastic cells along the instrument tract[1].

Canine prostate-specific arginine esterase (CPSE) is a serum protease secreted by prostatic epithelial cells which makes up more than 90% of the protein in the prostatic fluid and is present in seminal blood and plasma[3,8]. Recent studies have demonstrated a positive correlation between the serum concentration of CPSE and abnormal prostatic growth[8,9]. Due to this relationship, CPSE may be an alternative method of screening dogs to identify pre-clinical prostatic disease, especially BPH[3,8,9]. Although CPSE concentrations may be used to identify early prostatic disease, its diagnostic value is limited due to its concentration being affected by multiple prostatic diseases such as BPH, prostatic carcinoma, and prostatitis[8]. The Odelis CPSE™, a commercial enzyme-linked immunosorbent-type immunoassay made by Virbac, has been developed for the purpose of diagnosing BPH from a blood sample. The assay reportedly has a sensitivity of 97.1% and a specificity of 92.7%; however, it is not commercially available in the United States at this time[3,10].

Treatment and Management Options

Treatment of BPH is aimed at decreasing the prostatic concentration of androgens, specifically DHT, thereby eliminating the primary factor influencing prostatic growth. The gold standard of therapy is surgical castration which completely removes all androgenic stimulation

and causes a 50-70% reduction in prostate size by 3 weeks post-castration and complete involution by 4 months[1,3,4]. For dogs that cannot be neutered, whether due to anesthetic concerns or because of their use as a breeding animal, various medical therapies are available.

Finasteride is a synthetic steroid type-II 5α-reductase inhibitor and is the most common medical therapy utilized to treat BPH in dogs[1,3,11]. Finasteride inhibits the conversion of testosterone to DHT which consequently decreases the production and expression of prostate growth factor. Without androgenic influence, the hyperplastic cells of the prostate undergo apoptosis thus reducing prostatic volume by up to 70% after 16 weeks of treatment[1,3]. Reduction of DHT by finasteride also contributes to reduction of prostatic vascularization via decreased expression of vascular endothelial growth factor (VEGF-A)[11]. The use of finasteride causes a significant reduction in the third fraction but has no effect on libido or spermatogenesis[1,3]. Finasteride is dosed at 0.1-0.5 mg/kg PO every 24 hours for 16 weeks (not to exceed 5mg per dog per day). Treatment can then be tapered to every 2 to 3-day administration but must be continued for the life of the dog or until castration. If treatment is discontinued in an intact dog, prostatic hyperplasia and clinical signs will re-occur[1,3].

Tamoxifen is synthetic nonsteroidal Type I antiestrogenic compound which competitively blocks estrogen receptors with a mixed antagonist-agonist effect[12]. Its primary use is for the treatment of breast cancer in women; however, it has been used empirically for the treatment of BPH in dogs[3,12]. In a study by Corrada et al., tamoxifen, given at a dose of 2.5 mg PO every 24 hours for 28 days, decreased prostatic volume by 50% while also causing the volume of the third fraction to decrease to a few drops or absent[12]. During treatment, tamoxifen also caused significant decreases of testicular size, libido, serum testosterone concentration, and spermatozoal motility and normal morphology. After discontinuation of therapy, all parameters

gradually returned to pretreatment levels and 3 of the male dogs were able to sire normal litters. No systemic side effects were observed during treatment. With the information available at this time, tamoxifen may represent a rapid and reversible treatment option for BPH; however, due to the impacts on sperm production, animals would not be able to breed while being treated[3,12].

Anastrazole is an aromatase inhibitor which blocks the synthesis of estrogens by preventing the conversion of androgens to 17β-estradiol[3,5,13]. Like tamoxifen, anastrazole's primary use is the treatment of breast cancer in women; however, it has also been found to be effective in the treatment of canine BPH. In a study by Gonzalez et al., anastrazole, given at a dose of 0.25 – 1.0 mg per dog PO every 24 hours for 28 days, decreased prostatic volume by 21% without causing any significant changes in libido, scrotal diameter, testicular consistency, semen volume, motility, count, or morphologic abnormalities. There were also no hematologic or other clinical adverse reactions noted during the study[13]. With the limited information available, anastrazole may present veterinary practitioners with a more rapid alternative to BPH treatment without adversely affecting fertility.

Medroxyprogesterone acetate is a progestin which has been used to treat BPH because of its antiandrogen activity which is possibly due to competitive binding with androgen receptors and/or suppression of luteinizing hormone secretion via negative feedback at the level of the hypothalamus[1,3]. Medroxyprogesterone acetate has been shown to decrease clinical signs of BPH in 84% of dogs and decrease prostatic volume in approximately 53% of patients after 6 weeks of treatment[3]. While effects on semen quality and libido have not been evaluated, concerns of its use causing mammary nodules, diabetes mellitus, and hypothyroidism have prevented it from being regularly used as a treatment for BPH[1,3].

Case Outcome

On May 13, 2019, thoracic radiographs were performed to evaluate for any cardiopulmonary changes due to heartworms. No changes were seen, so on May 15, 2019, Woody was placed under general anesthesia and castrated at MSU-CVM. He was discharged that same afternoon with 75mg carprofen to be given by mouth every 12 hours for 4 days for control of pain and inflammation. He was also sent home with an e-collar with instructions to wear it for the next 10-14 days while the incision healed and instructions to monitor the incision site for swelling and signs of infection. On May 24, 2019, Woody's owner reported that he was feeling better than he had in a long time and he was "like a new dog". On April 7, 2020, Woody finally tested negative for heartworms.

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