

# Cytology of the canine prostate

Michelle Kraft, Holly M. Brown and Bruce E. LeRoy

Department of Pathology, College of Veterinary Medicine, University of Georgia, Athens, GA 30602-7388, USA

## Introduction

Diseases of the prostate are common in middle-aged to older intact male dogs. The canine prostate can be affected by benign prostatic hyperplasia (BPH), squamous metaplasia, cysts, infection and neoplasia (which affects neutered as well as intact dogs). While histopathologic diagnosis of prostatic disease allows detailed evaluation of tissue architecture, cytologic evaluation of the prostate is also a valuable diagnostic technique. Advantages of performing cytology over prostatic biopsy and histopathology include: reduced invasiveness; minimal sedation; and rapid result reporting (Powe *et al.*, 2004). While previous work has shown that there is a high (80%) concordance between cytologic and histologic diagnoses of prostatic disease (Powe *et al.*, 2004), the thin monolayer obtained with cytologic smears often allows better assessment of individual cytomorphology, as well as improved detection of aetiologic agents.

Prostatomegaly, detected during digital rectal examination (DRE) or with imaging such as radiography or ultrasonography, is an indication for obtaining fine needle aspirates from the canine prostate. Clinical signs of prostatic disease, including dysuria, dyschezia and haematuria, are also important indications for obtaining material from the gland for microscopic examination. Cytologic samples may be obtained through the urethra or by fine needle aspiration of the gland (Zinkl 1999). This article reviews diagnostic procedures and expected cytologic findings for the most common prostatic disorders encountered in small animal practice.

## Sampling techniques

The three most common and effective sampling techniques include collection of ejaculate fluid, fine needle aspiration (often utilising ultrasound guidance), and urethral catheterisation with prostatic massage. The sample cellularity and subpopulations of prostatic cells obtained will vary depending on the collection technique (Zinkl, 1999).

### *Ejaculate fluid*

Ejaculate fluid is obtained by manual manipulation of intact male dogs. The third fraction of the ejaculate, which is the clear prostatic fluid, should be collected separately from the rest of the fluid (Barsanti and Finco, 1995). Approximately 0.5 ml to 1 ml of fluid is adequate for cytological and microbiological examination. Direct smears and cytocentrifuge preparations should be evaluated. If

inflammation is suspected, an aliquot of the fluid should be placed in a vial containing EDTA for cytologic examination (Baker and Lumsden, 2000). A separate sample of the fluid should be placed in an EDTA-free container for culture and sensitivity, as EDTA may interfere with bacterial growth in culture systems. Dogs with painful prostatic diseases are usually not able to be collected.

### *Fine needle aspiration*

Fine needle aspiration of the prostate gland under ultrasound guidance is an effective means of localising and diagnosing prostatic lesions (Zinkl, 1999). In dogs that present with signs of septic prostatitis (e.g., fever, inflammatory leukogram, painful digital rectal examination), consideration should be given to the possibility that fine needle aspiration could seed an infection along the needle tract and lead to peritonitis (Zinkl, 1999). If sampling has already begun and purulent fluid is noted, aspiration should continue until all pressure is reduced to prevent leakage of the material (Baker and Lumsden, 2000). It should be noted that with ultrasound-guided fine needle aspiration, the ultrasound gel can contaminate the cytologic specimen. This gel appears as small, deeply magenta-coloured granular to occasionally rod-shaped structures found scattered throughout the cytologic preparation. To avoid this artifact, excess gel should be removed from the skin prior to aspiration (Zinkl, 1999).

### *Prostatic massage*

Prostatic massage combined with urethral catheterisation can be performed if the dog is unable to ejaculate and ultrasound is unavailable. This technique is especially useful in identifying neoplastic cells (Cowan and Barsanti, 1991). The preferred method is to pass a urinary catheter guided by rectal palpation to the prostatic urethra. A syringe is attached to the end of the catheter and aspirated while simultaneously massaging the prostate through the rectum. If only a small fluid sample is obtained, a few millilitres of saline can be flushed into the catheter while the prostate is massaged and fluid may be re-aspirated with a syringe (Olson *et al.*, 1987).

## Normal cytological findings

Cytologic findings from normal canine prostate glands will vary depending upon the sampling technique used. Normal prostatic ejaculate is clear and may contain a few erythrocytes, leukocytes and squamous epithelial cells (Powe *et al.*, 2004). A few contaminant organisms may

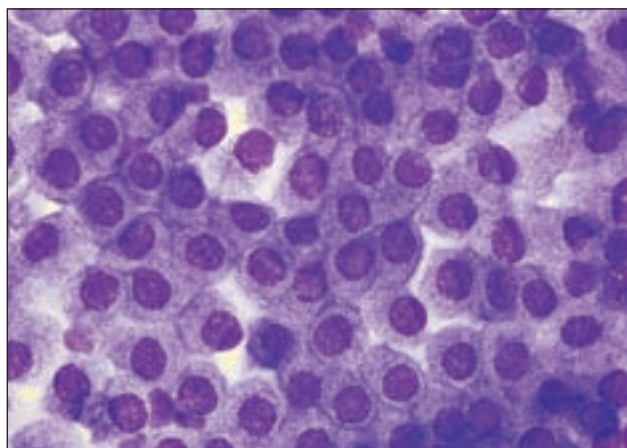


Figure 1: Fine needle aspirate from a normal canine prostate gland containing uniform sheets of well-differentiated polyhedral cells with a granular, eosinophilic cytoplasm. Nuclei are round and contain coarse granular chromatin. (Wright-Leishman stain; 50x magnification).

be present in association with squamous epithelial cells. Additionally, ejaculate samples may contain numerous spermatozoa and cells originating from the reproductive tract and urethra (Zinkl, 1999). Spermatozoa will stain blue-green with Wright's stain and may be adherent to other cells (Raskin and Meyer, 2001). Healthy dogs are reported to have less than 100 bacteria/ml of prostatic fluid; however, undetected urethral contamination may account for up to  $10^5$  bacteria/ml without evidence of inflammation (Barsanti and Finco, 1995). Most contaminant bacteria are Gram-positive. Large numbers of Gram-negative bacteria and degenerate neutrophils with intracytoplasmic bacteria are indicative of infection (Dorfmann and Barsanti, 1995). Fine needle aspirates of a normal prostate gland commonly contain clusters of well-differentiated cuboidal to low columnar prostatic epithelial cells (Figure 1). The epithelial cytoplasm is finely granular and basophilic and may be vacuolated. Nuclei are round to oval with a single small, inconspicuous nucleolus (Baker and Lumsden, 2000). Cells may exfoliate in sheets that have a 'honeycomb' appearance. The identification of squamous epithelial cells from fine needle aspiration supports a diagnosis of squamous metaplasia or squamous cell carcinoma, whereas these same cells in fluid samples obtained from prostatic massage likely represent normal lower urinary tract squamous epithelial cells.

Prostatic massage samples from normal dogs contain spermatozoa, transitional epithelial cells, squamous epithelial cells and erythrocytes. Only rarely are well-differentiated prostatic epithelial cells or bacteria noted in pre- or post-massage samples (Barsanti *et al.*, 1980). Additionally, cultures of prostatic fluid from prostatic massage are expected to yield minimal bacterial growth, the source of which is likely lower urethral contamination (Baker and Lumsden, 2000).

## Non-neoplastic disease

### Benign prostatic hyperplasia

Benign prostatic hyperplasia (BPH) is a common disorder in older intact male dogs. It is associated with an increase in size and weight of the prostate gland due to increases in

interstitial tissue and gland lumens (Lowseth *et al.*, 1990). BPH is androgen-dependent and therefore does not occur in castrated dogs (Dorfman and Barsanti, 1995). Though older intact male dogs will have decreased testosterone production, androgen receptor density on the target cell membrane is increased in hyperplastic tissue, resulting in heightened sensitivity to circulating androgens (Raskin and Meyer, 2001). Oestrogens may also act synergistically with androgens in potentiating BPH (Olson *et al.*, 1987). Clinical signs associated with BPH include a haemorrhagic, non-suppurative urethral discharge as well as faecal tenesmus, as the enlarged prostate often impinges on the descending colon and/or rectum (Baker and Lumsden, 2000). Palpation of the prostate usually reveals a symmetrically enlarged, non-painful gland (Raskin and Meyer, 2001).

Cytology of BPH reveals epithelial cells arranged individually or in variably sized clusters. Occasionally, a few clusters may have an acinar-like arrangement with indistinct cytoplasmic borders (Zinkl, 1999). The epithelial cells are well-differentiated and very similar in appearance to normal prostatic epithelial cells but may exhibit a characteristic mosaic appearance with uniform cell size, abundant basophilic cytoplasm and mature nuclei with a small, round nucleolus (Baker and Lumsden, 2000). The nuclei are round to oval with finely reticulated or stippled chromatin patterns (Zinkl, 1999). There may be an increase in cell size and mild anisokaryosis, but the nucleus:cytoplasm (N:C) ratio is preserved. In a sample obtained by prostatic massage, the cellularity may be increased (Baker and Lumsden, 2000). Therefore, a symmetrically-enlarged prostate with cytology yielding clumps of well-differentiated prostatic epithelial cells without inflammation is consistent with a diagnosis of BPH (Raskin and Meyer, 2001).

### Squamous metaplasia

Squamous metaplasia occurs when epithelial stem cells are induced to differentiate along a new developmental pathway (Cotran *et al.*, 1999). In the prostate, this is manifested by the replacement of cuboidal to low-columnar prostatic epithelial cells with squamous epithelial cells which characteristically appear as large, flattened, slightly basophilic cells. Oestrogen receptors on ductal, stromal and approx. 10% of prostatic epithelial cells mediate this response (Baker and Lumsden, 2000). The oestrogen source in male dogs is usually a Sertoli-cell tumour in an undescended abdominal testicle or treatment with exogenous oestrogens; however, chronic irritation and inflammation can also result in squamous metaplasia (Zinkl, 1999; Raskin and Meyer, 2001). Hyperoestrogenism may also cause affected dogs to develop bilateral symmetrical endocrine alopecia, dermal hyperpigmentation, gynecomastia and a pendulous prepuce (Raskin and Meyer, 2001; Feldman and Nelson, 2004). Pancytopenias and bone marrow hypoplasia are also commonly noted in hyperoestrogenism (Feldman and Nelson, 2004). Prostatic aspirates from dogs with squamous metaplasia are

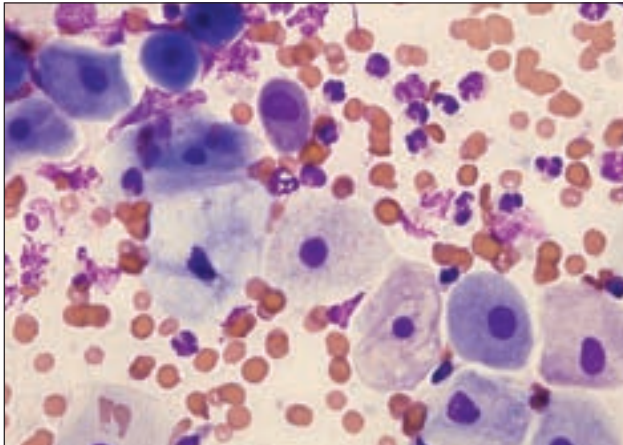


Figure 2: Fine needle aspirate from a canine prostate with squamous metaplasia. The smear contains numerous well-differentiated squamous cells with varying degrees of keratinisation. Most squamous cells exhibit a low nucleus: cytoplasm ratio and contain abundant pale to basophilic cytoplasm. Mild suppurative inflammation and blood contamination are also present. (Wright-Leishman stain; 50x magnification).

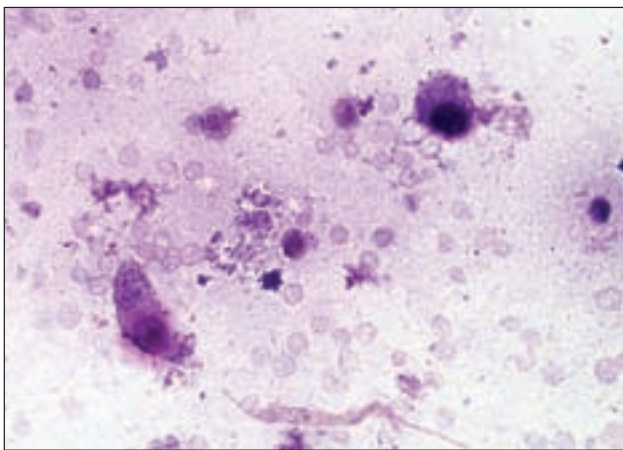


Figure 3: Fine needle aspirate from a prostatic cyst. The smear is poorly cellular and contains a finely-granular, pale magenta-coloured background material (cystic fluid) with scattered erythrocytes and a few well-differentiated prostatic epithelial cells. (Wright-Leishman stain; 50x magnification).

usually moderately cellular and composed of large, well-differentiated squamous epithelial cells that contain slightly basophilic to slightly acidophilic cytoplasm and exhibit a low N:C ratio (Figure 2). They are arranged singly or in clusters and may appear flattened or folded (Zinkl, 1999). They may be intermixed with larger single epithelial cells containing a low to moderate N:C ratio (Baker and Lumsden, 2000) and may occasionally have pyknotic or karyorrhectic nuclei. These larger cells are often found at the feathered edge of the smear. In addition, inflammatory cells, bacteria, haemorrhagic debris such as haemosiderin and haematoidin as well as intact red blood cells may be found if prostatic abscesses and cysts are also present (Zinkl, 1999; Baker and Lumsden, 2000).

#### Prostatic cysts

Prostatic cysts (Figure 3) account for only 2-5% of canine prostatic abnormalities (Dorfmann and Barsanti, 1995). They can occur as multiple cysts associated with benign prostatic hyperplasia or squamous metaplasia, or they may occur singly as intraprostatic or paraprostatic cysts. Large, discrete cysts may be palpated in the caudal abdomen or in the perineal area. Clinical signs, when present, may

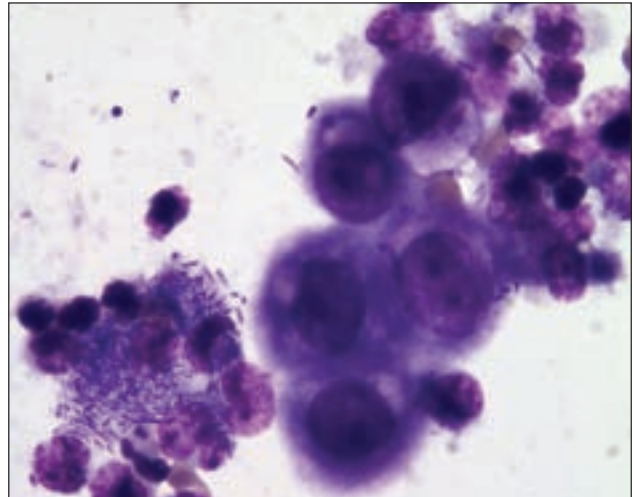


Figure 4: Fine needle aspirate of septic, suppurative prostatitis. The smear contains clumps of well-differentiated hyperplastic prostatic epithelium with numerous degenerate neutrophils and intracellular bacterial rods. (Wright-Leishman stain; 50x magnification).

include bloody urethral discharge, dysuria and tenesmus (when the cysts result in increased prostatic size). However, clinical signs are uncommon unless the cyst or cysts become secondarily infected (Henson, 2001).

Grossly, fluid obtained from urethral discharge or aspiration of prostatic cysts may appear serosanguinous to brown. Microscopically, the fluid may be acellular or contain a few erythrocytes, leukocytes or benign epithelial cells (Baker and Lumsden, 2000). Occasionally, small numbers of slightly hyperplastic epithelial cells (interpreted to be cyst lining cells) are present. Squamous cells are rarely observed. The specific gravity and protein concentration of prostatic cyst fluid are usually similar to a transudate (low protein concentration and low cellularity) (Zinkl, 1999).

#### Prostatitis

Bacterial infections are implicated in 20%-70% of dogs with clinical signs of prostatic disease (Cowan and Barsanti, 1991), usually ascending from the prostatic urethra. Bacteria are not normally present in the canine prostate gland. Organisms frequently isolated include: *Escherichia coli* (most commonly); *Proteus* spp.; *Staphylococcus* spp.; and *Streptococcus* spp. (Dorfmann and Barsanti, 1995). Most instances of prostatic infection occur in association with urinary tract infection or due to altered prostatic architecture secondary to squamous metaplasia or cysts. Foci of infection may also be found in neoplastic prostate glands, although the dogs may not show clinical signs of prostatitis. These conditions predispose the prostate to infection by providing a medium for bacterial growth or by interfering with normal defence mechanisms (Baker and Lumsden, 2000). In addition, haematogenous infection may occur.

Prostatitis may be acute or chronic in nature. Clinical signs of acute prostatitis include systemic signs of illness such as fever, lethargy and anorexia, in addition to purulent urethral discharge and a painful gland (enlargement of the gland is not commonly associated with acute prostatitis).

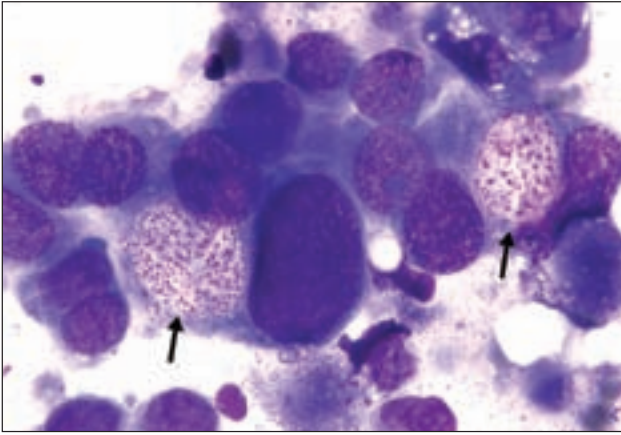


Figure 5a: Fine needle aspirate from a prostatic carcinoma. The smear contains a densely cellular clump of anaplastic prostatic epithelial cells with significant anisocytosis and anisokaryosis. Two of the cells contain large secretory vacuoles filled with a granular, eosinophilic material (arrows). (Wright-Leishman stain; 50x magnification).

An inflammatory leukogram, with or without a left shift, is often present (Henson, 2001). Chronic prostatitis, in contrast, often presents as recurrent urinary tract infections. Signs of systemic illness are usually not present, but the dog may have intermittent or constant urethral discharge. If areas of septic prostatitis coalesce or if prostatic cysts become infected, an abscess may develop. If an abscess ruptures, systemic illness related to endotoxemia or peritonitis may occur (Baker and Lumsden, 2000). Cytologic evaluation of acute prostatitis reveals predominantly degenerate neutrophils often with detectable intracellular bacteria (Figure 4). In addition to neutrophils, cytology of chronic prostatitis often reveals large numbers of macrophages along with lymphocytes and plasma cells. If antimicrobial therapy has not been administered, intracellular and extracellular organisms may be seen. A few hyperplastic epithelial cells with increased cytoplasmic basophilia, increased N:C ratios and mild anisokaryosis may also be present (Henson, 2001). A cytologic diagnosis of neoplasia in the presence of severe inflammation may be challenging, as inflammation can induce numerous cytologic criteria of malignancy in normal or hyperplastic cells (Baker and Lumsden, 2000).

### Neoplastic disease

Prostatic carcinoma in dogs is uncommon (found in only 0.2%-0.6% of dogs in necropsy studies) (Bell *et al.*, 1991) and occurs most frequently in neutered and intact male dogs ranging from eight to 10 years of age. Among dogs with prostatic disease, however, one study showed that 16% were diagnosed with adenocarcinomas (Olson *et al.*, 1987). In addition to prostatic carcinoma, transitional cell carcinoma may also involve the prostatic urethra and prostate gland. It is difficult to determine the cell of origin of canine prostatic carcinomas, as there is no specific molecular marker that will distinguish prostate epithelium from transitional epithelium (LeRoy *et al.*, 2004). Additionally, some have hypothesised that canine prostatic carcinomas originate from the prostatic ductal epithelium instead of the secretory epithelium of prostatic acini (Leav *et al.*,

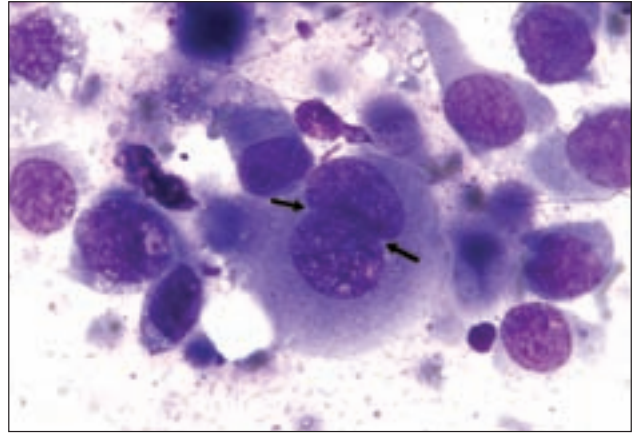


Figure 5b: Fine needle aspirate from a prostatic carcinoma. Nuclear moulding (arrows) is detected in the epithelial cells in the centre of the image. (Wright-Leishman stain; 100x magnification).

2001). Digital rectal examination of prostate tumours commonly reveals an enlarged, irregularly asymmetrical, usually non-painful, gland (Zinkl, 1999). Clinical signs may include tenesmus, dyschezia, anorexia and weight loss. Many present with quite advanced disease, as dogs often do not show clinical signs until late in the course of the malignancy (Henson, 2001). As a result, the disease carries a poor prognosis; survival times in treated and untreated dogs are usually less than two months (Bell *et al.*, 1991). Prostatic carcinomas are highly metastatic and commonly spread to iliac and sublumbar lymph nodes, as well as to distant organs, such as the lungs, urinary bladder, mesentery and bone. Bone metastases are most often located in the pelvis, lumbar vertebrae and femur and may be osteolytic, osteoblastic, or mixed (Dorfmann and Barsanti, 1995; Zinkl, 1999). The bone metastases may cause lumbar pain along with posterior paresis or paralysis due to pathologic fractures or impingement of tumour-induced new bone formation on nerve roots.

Aspirate smears from prostatic carcinomas are usually highly cellular and composed of deeply basophilic, anaplastic polyhedral to round cells arranged in variably-sized sheets and clusters (Figure 5a and 5b). The epithelial cells contain abundant, deeply basophilic cytoplasm and often contain numerous large, round, poorly-staining cytoplasmic vacuoles (Baker and Lumsden, 2000). The N:C ratio is moderate to high and anisokaryosis, nuclear enlargement and irregularity of the nuclear membrane can be found (Henson, 2001). Nucleoli are multiple and prominent (Barsanti and Finco, 1984). Cell membranes in well-differentiated neoplasms may be distinct but are often not well visualised in poorly differentiated tumours.

### Treatment

- Benign prostatic hyperplasia: The most effective treatment for benign prostatic hyperplasia is castration, which results in a marked reduction in prostate size as well as clinical signs within a few weeks of surgery (Barsanti and Finco, 1995).
- Squamous metaplasia: Treatment is aimed at removing the oestrogen source, which is usually a Sertoli-cell

tumour in an undescended testicle (Zinkl, 1999).

- Prostatic cysts: Cysts may be surgically removed or paraprostatic cysts may be marsupialised, but both treatments may result in surgical complications (Baker and Lumsden, 2000). Intact dogs should be neutered.
- Prostatitis: Treatment involves appropriate antibiotic therapy as determined by bacterial culture and sensitivity performed on prostatic fluid samples. In acute prostatitis, most antibiotics will penetrate to the site of the infection due to disruption of the prostate-lipid barrier (Olson *et al.*, 1987). In chronic prostatitis, however, this barrier is usually considered to be functional and antibiotics should be selected for their lipid solubility and tendency to concentrate in the prostate (Olson *et al.*, 1987). If an abscess is present, it may be treated surgically. Castration is also beneficial (Dorfmann and Barsanti, 1995).
- Prostatic carcinoma: Treatment is usually palliative therapy and may include the use of cyclooxygenase inhibitors such as piroxicam. Prostatectomy or intraoperative radiation may be performed.

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Reprint requests to: Dr Bruce LeRoy, Room 114, Department of Pathology, University of Georgia, 501 DW Brooks Drive, Athens, GA 30602-7388, USA.