All Lesions Great and Small, Part 2. Diagnostic Cytology in Veterinary Medicine

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This is the second in a two-part review of diagnostic cytopathology in veterinary medicine. As in human medicine, cytopathology is a minimally invasive, rapid, and cost-effective diagnostic modality with broad utilization. In this second part, the diagnostic applications of cytology in respiratory, gastrointestinal, genitourinary, endocrine, ocular, and central nervous system tissues are discussed with a section describing fluid analysis in veterinary medicine. As noted in the previous manuscript, which characterized the cytology of the skin/subcutis, musculoskeletal, and lymphoid tissues, the interpretation of veterinary cytology samples must be undertaken with extensive knowledge of the breadth of animal species, including familiarity with the frequency and clinical progression of diseases, both of which can be influenced by species, breed, and husbandry conditions. Similar to part one, this review focuses on the most common domestic companion animal species (dog, cat, and horse) and highlights lesions that are either unique to veterinary species or have relevant correlates in people. The cytologic features and biological behavior of similar lesions are compared, and selected mechanisms of disease and ancillary diagnostics are reviewed when appropriate. Supporting figures illustrate a subset of lesions. While not an exhaustive archive of veterinary cytology, the goal is to give cytopathologists working in human medicine a general impression of correlates and unique entities in veterinary practice. Diagn. Cytopathol. 2014;42:544–552.

Key Words: veterinary; cytology; neoplasia; infectious disease; dog; cat

This manuscript is the second in a two-part series providing an overview of diagnostic cytopathology in veterinary medicine. Some unique features of the practice of veterinary medicine that impact utilization of cytology, such as limited communication between the clinician and "patient," the need for anesthesia for restraint to pursue more invasive sample collection procedures, and financial factors were reviewed in the preceding article. Likewise, extensive knowledge of species-specific anatomy, physiology, and the prevalence and prognosis of disease is a prerequisite for the practice of veterinary cytopathology. The previous companion paper reviewed the cytologic diagnosis of the most commonly sampled tissues in general practice, including lesions of the skin and subcutis, the musculoskeletal system, and lymphoid tissues. This review will focus on the remaining organ systems and fluid analysis, which in aggregate form an important body of diagnostic information, particularly in specialty veterinary practice. In parallel to the first manuscript, the emphasis will be on common lesions, those with correlates in human medicine, and will highlight unique entities in veterinary medicine so as to give the reader a general impression of veterinary cytopathology.

Respiratory Tissues

The most common respiratory tissue samples evaluated by veterinary cytolopathologists include those from the nasal cavity (usually swabs, flushes, or aspirates), the upper and lower airways (in the form of tracheal washes, bronchoalveolar lavages [BAL]), and lung aspirates. Normal nasal cytology samples in most species are of low cellularity and are comprised of squamous and ciliated columnar epithelial cells accompanied by epicellular and extracellular commensal bacteria, while nasal associated lymphoid tissue and mucus can also be present. Nasal disease is relatively common in domestic species and is often of either infectious (typically bacterial or fungal) or neoplastic origin. Bacterial rhinitis in dogs and cats is often secondary to the presence of other inflammatory/infectious disease or neoplasia, so superficial samples can

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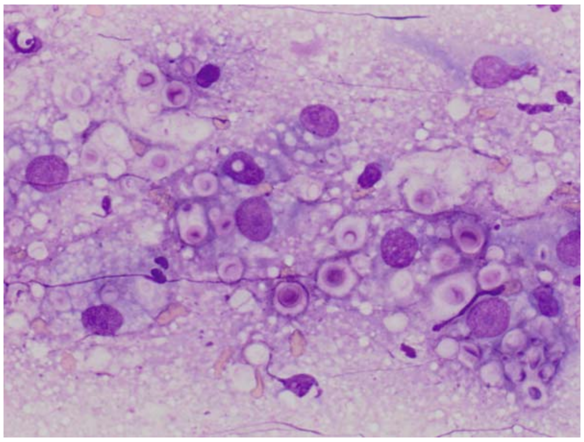

Fig. 1. Cryptococcosis. Cat. Nasal cytology. Sample contains numerous round to oval, eosinophilic staining yeasts with a thick clear capsule. Macrophages and a few neutrophils are also present (Wright–Giemsa, ×500). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

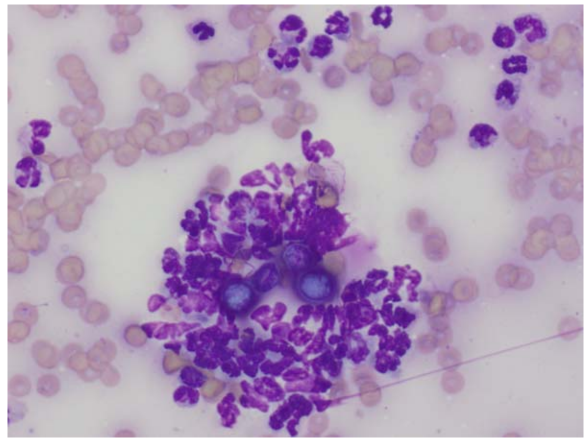

Fig. 2. Blastomycosis. Dog. Lung aspirate. Round, dark-basophilic, thick-walled yeast forms of *Blastomyces dermatitidis* showing broad-based budding are surrounded by numerous neutrophils (Wright–Giemsa, ×500). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

be diagnostically misleading. In contrast, fungal rhinitis due to *Aspergillus* and *Penicillium* sp. in dogs or *Cryptococcus* sp. in cats can be primary, however, low numbers of fungal elements can be present in clinically normal dogs and cats (Fig. 1). Unique to horses are bacterial or fungal infections of the guttural pouches, which are paired, air-filled, auditory tube diverticula connecting the nasopharynx to the middle ear and, when infected may present with purulent or bloody nasal discharge as the primary complaint. Because of their complex anatomy, which includes their juxtaposition to several cranial nerves and the internal and external carotid arteries, diseases of the guttural pouch, particularly those of bacterial and fungal origin, can result in significant neurologic dysfunction or fatal hemorrhage.[1]

The cytologic diagnosis of nasal neoplasia can be complicated by concurrent inflammation and dysplasia. However, a large, retrospective, canine cytology–histology correlation study demonstrated the utility of cytology in discriminating neoplastic from non-neoplastic processes in 86% of 138 dogs, with good concordance for the subclassification of tumors as carcinomas (most common), sarcomas, and round cell tumors (least common).[2]

Lower respiratory tract cytology is often performed to identify infectious, inflammatory, or neoplastic pulmonary disease, although occasionally these samples will reveal evidence of hemorrhage, often due to anticoagulant rodenticide poisoning in dogs or exercise-induced pulmonary hemorrhage in horses. It is particularly noteworthy that airway samples from indoor-housed horses may contain a variety of fungal hyphal fragments, spores, and macroconidia, which are generically referred to as "barn fungus" and considered contaminants of the airway tract rather than true pathogens. Overall, infectious pulmonary disease exhibits a similar spectrum of organisms as in people, with similar regional variation. In the Upper Mid-West, pulmonary blastocymosis is an important cause of canine respiratory disease and dogs are monitored as a sentinel species for human infection, although infected dogs are not considered a zoonotic risk (Fig. 2). Pulmonary neoplasia, both primary and metastatic, is most common in dogs and cats and rare in the horse. Cytologic evaluation of either BAL or lung aspirates is capable of detecting multiple types of lung carcinoma, although tumor origin (primary vs. metastatic) or subtype cannot be distinguished cytologically. The lung can also be a primary site for hematopoietic neoplasia, including lymphoma and histiocytic sarcoma (Fig. 3).

Gastrointestinal System

Oral lesions can be cytologically sampled, although this usually requires sedation or anesthesia (Figs. 4 and 5). Systematic studies are lacking, but with the advancement of veterinary dentistry, there is opportunity for additional utilization of cytology to screen lesions, with a prospective study underway at our institution. Cytologic evaluation of the remainder of the gastrointestinal tract is usually performed on impression smears of endoscopically collected mucosal biopsies or ultrasound guided FNA samples of mass lesions. Cytology is most useful for the detection of some infectious agents (e.g., histoplasmosis) and in the diagnosis of certain intestinal neoplasms (e.g., lymphoma and adenocarcinoma). The architectural benefits of full-thickness section histopathology make it preferred over cytology for distinguishing lymphocytic inflammation from lymphoma in the diagnosis of idiopathic inflammatory bowel disease, which is common in both dogs and cats.

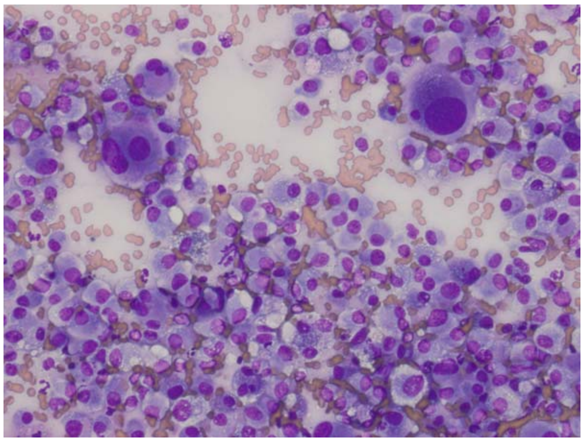

Fig. 3. Histiocytic sarcoma. Dog. Lung mass aspirate. Numerous round cells with a large amount of basophilic cytoplasm that is variably vacuolated. A single round to oval nucleus is present in most cells, but some have multiple variably sized nuclei. Marked anisocytosis and anisokaryosis can be seen. A mitotic figure is present just left of center (Wright–Giemsa, ×200). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

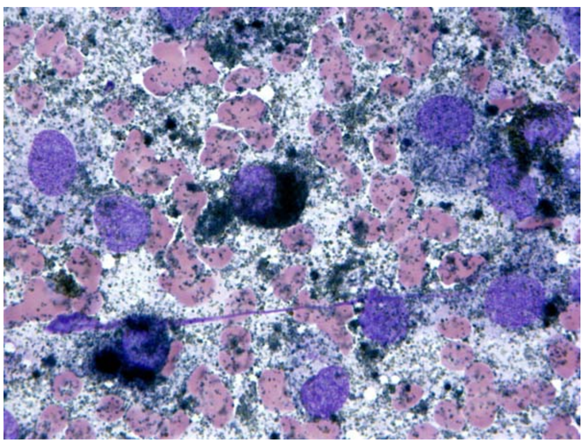

Fig. 4. Melanoma. Dog. Oral mass aspirate. Neoplastic melanocytes characterized by rounded cell margins that contain a moderate to large amount of cytoplasm and a single large, round to oval nucleus. Melanocytes have moderate to large amounts of intracytoplasmic dark pigment. These same pigment granules can also be seen scattered throughout the background. Anisocytosis and anisokaryosis are moderate (Wright–Giemsa, ×1,000). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

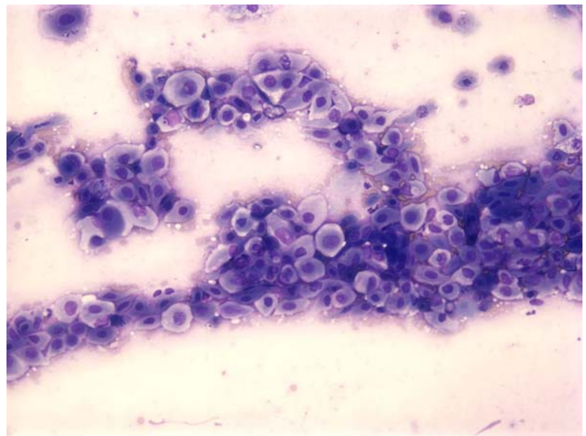

Fig. 5. Squamous cell carcinoma. Cat. Oral mass aspirate. Numerous neoplastic squamous epithelial cells characterized by rounded to angular cell margins that contain a moderate to large amount of basophilic, keratinized appearing cytoplasm and a single round to oval nucleus. Anisocytosis and anisokaryosis are moderate and nuclear to cytoplasmic ratios are variable. Some cells have keratinized cytoplasm with retained nuclei (asynchronous cytoplasmic and nuclear maturation) (Wright–Giemsa, ×200). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Fine-needle aspiration cytology of the liver is used very frequently in dogs and cats to evaluate elevated serum enzyme activities, investigate ultrasonographic abnormalities, and as part of the staging process for many neoplasms. Cytology is accurate for the detection of the hepatocyte vacuolar changes that, while often nonspecific, can accompany certain endocrinopathies, including diabetes mellitus and hyperadrenocorticism. In the cat, marked lipid vacuolar change accompanied by suggestive serum biochemical abnormalities is highly diagnostic for feline hepatic lipidosis, a metabolic syndrome triggered by acute anorexia that can be idiopathic, stress-induced, or secondary to other diseases (Fig. 6). For the diagnosis of hepatic neoplasia, cytology has moderate sensitivity but very good specificity and positive predictive value, including accurately classifying round cell tumors and hepatocellular and non-hepatocellular carcinomas.[3] In contrast, cytology has both low sensitivity and positive predictive value for inflammatory liver disease, in which case histopathology is recommended for definitive diagnosis.[4] Despite the importance of pancreatitis in both dogs and cats, concerns about the safety of sampling that organ have delayed the validation of pancreatic cytology as a diagnostic tool. Several small studies and one larger one suggest cytologic sampling of the pancreas is a low-risk procedure, which should promote further validation of this technique.[5,6]

Genitourinary Tissues

The cytologic evaluation of companion animal reproductive tissues is generally restricted to the canine prostate gland, as sampling of ovary and testes is relatively uncommon because most veterinary patients are spayed or neutered. Enlargement of the canine prostate gland can result from inflammatory, benign hyperplastic, or malignant neoplastic causes. Canine benign prostatic hyperplasia is common in older, male dogs, but because of anatomic variation between species, prostatic enlargement usually results in constipation and tenesmus rather than dysuria.[7] Cytology of hyperplastic prostatic epithelium is characterized by sheets of “honeycomb” appearing cells with minimal atypia (Fig. 7). It is noteworthy that the

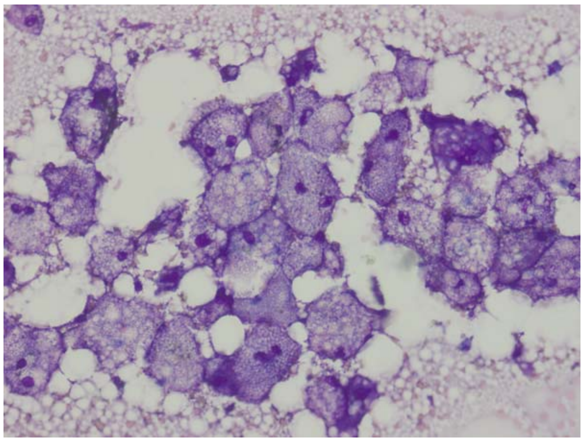

Fig. 6. Hepatic lipidosis. Cat. Liver aspirate. Cluster of hepatocytes with cells characterized by markedly distended cell margins containing numerous small, discrete, clear vacuoles and one to two small, round nuclei. Numerous variably sized lipid vacuoles are also seen throughout the background (Wright–Giemsa, ×200). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

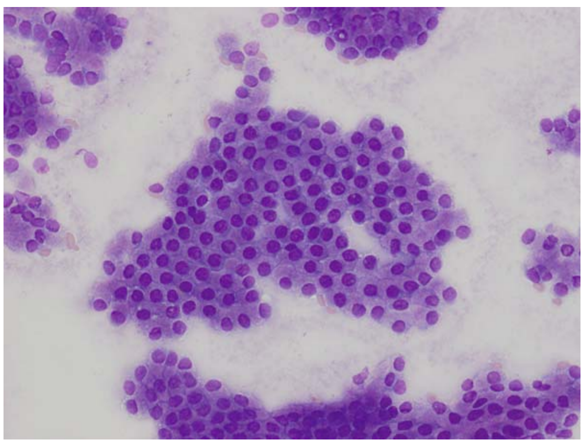

Fig. 7. Benign prostatic hyperplasia. Dog. Prostatic aspirate. Cohesive cluster of uniform prostatic epithelial cells with typical "honeycomb" appearance. These cells have a moderate amount of granular amphophilic cytoplasm with a single round nucleus. Anisocytosis and anisokaryosis are minimal (Wright–Giemsa, ×200). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

dog is the only other large mammal to develop spontaneous prostatic neoplasia at significant rates, which supports its usage as an animal model for human prostate cancer.[8]

Prostatic malignancy in dogs can be of either urothelial (transitional epithelial cell) or prostatic (acinar- or ductular-epithelial cell) origin. Although the two cannot be reliably distinguished by cytology or routine histology, both are characterized by sufficient criteria of malignancy that discrimination from benign prostatic hyperplasia is rarely problematic. One very unique neoplasm of the canine lower genital tract is the transmissible venereal tumor (TVT), which is one of only two known naturally

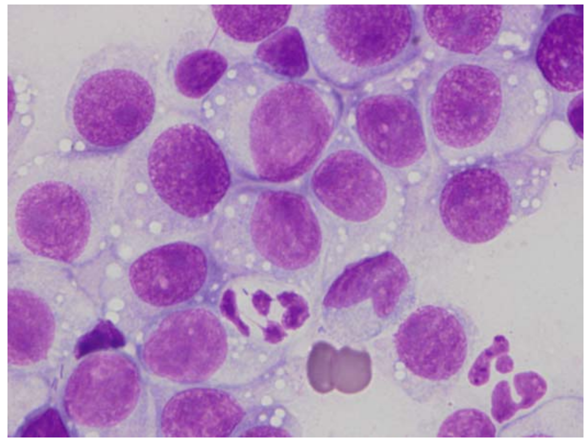

Fig. 8. Transmissible venereal tumor (TVT). Dog. Preputial mass aspirate. Discrete round cell population with cells characterized by a moderate amount of blue-gray cytoplasm that contains a single round nucleus with a coarse chromatin pattern and in some cases prominent nucleoli. Anisocytosis and anisokaryosis are moderate. Discrete, clear vacuoles are seen within the cytoplasm of most cells which is a characteristic feature of TVT, and can help to differentiate them from other round cell tumors. One of the neutrophils contains a single intracellular rod shaped bacterial organism. Septic inflammation is a common finding associated with these lesions (Wright–Giemsa, ×1,000). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

occurring, directly transmissible malignancies that clinically occurs as an exophytic mass on the perineum or the face and, epidemiologically, is considered enzootic in geographic regions with high numbers of free-roaming sexually intact dogs (Fig. 8). Genetic analysis supports a macrophage origin, and most tumors spontaneously regress, although immune-compromised individuals may require treatment.[9]

Cytologic evaluation of the urinary tract is primarily performed in dogs and cats with mass lesions or enlarged kidneys; cytology is not typically diagnostically useful for chronic renal disease or glomerulopathies.[10] Urinalysis is the mainstay of the diagnostic workup for mucosal disease of the bladder, but is beyond the scope of this review. Most renal FNAs are of low cellularity and normally contain blood and small clusters of well-differentiated cuboidal epithelial cells that in cats are often characterized by the presence of scattered lipid droplets. Fragments of cylindrical renal tubules are occasionally noted and rarely intact glomeruli may be observed. Cytologic samples can be used to support diagnoses of renal cysts, pyelonephritis, and other less-common infections of the kidney.

Although renal neoplasia is uncommon in dogs and cats, renal carcinoma is the most common variant. However, the cytologic and histologic differentiation of well-differentiated carcinomas from their benign, albeit less-common, counterparts can be difficult.[10] Nephroblastomas are sporadically reported in dogs and can be diagnosed cytologically[11]; these tumors occasionally present as

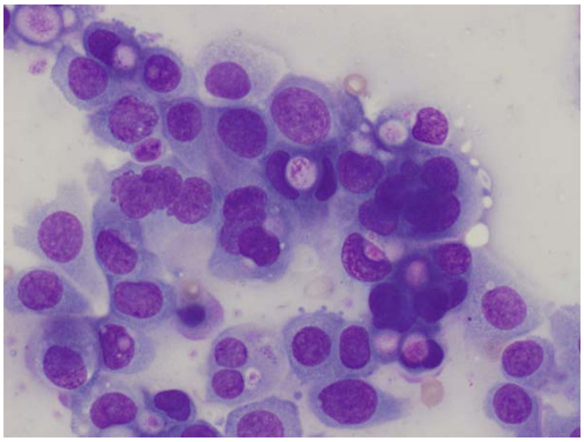

Fig. 9. Transitional cell carcinoma. Dog. Bladder mass aspirate. Loosely cohesive cluster of malignant transitional epithelial cells. These cells are round to polygonal and have a large amount of basophilic cytoplasm. Cells have one to multiple large, round to oval nuclei. Anisocytosis and anisokaryosis are marked. Several cells have large, round, eosinophilic, cytoplasmic inclusions that in some instances distort and peripheralize the nucleus (Wright–Giemsa, ×500). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

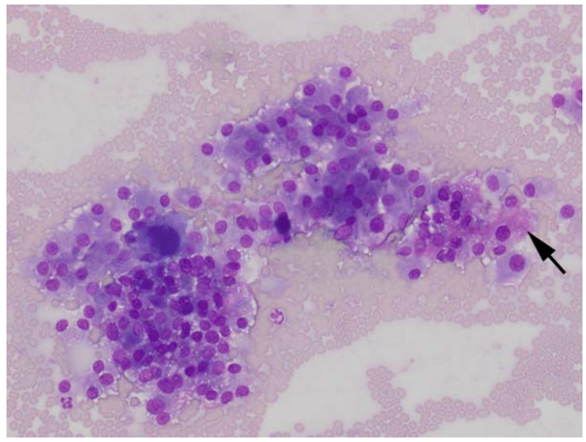

Fig. 10. Thyroid adenocarcinoma. Dog. Thyroid mass aspirate. Loosely cohesive clusters of thyroid epithelial cells. These cells are often disrupted or have indistinct cell margins that contain a moderate to large amount of basophilic cytoplasm and a single round nucleus. Anisocytosis and anisokaryosis are relatively mild. A small amount of extracellular eosinophilic material typical of colloid can be seen (arrow) (Wright-Giemsa, ×200). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

spinal cord lesions, in which immunohistochemical staining for the Wilms tumor-1 antigen can support the diagnosis.[12] Evaluation of enlarged kidneys for the presence of lymphoma may be the most common application of renal cytology in veterinary medicine, especially in cats.[5,6] Such samples are usually highly cellular, consisting of large numbers of large, atypical lymphoid cells that can occasionally appear to form sheets or clusters in dense areas of the smear. Evaluation of equivocal samples using PARR is possible but rarely necessary.

The most common tumor of the urinary bladder in dogs and cats is transitional cell carcinoma, which is readily diagnosed cytologically and characterized by highly exfoliative but loosely cohesive sheets of large cuboidal to polyhedral to spindloid cells characterized by dramatic criteria of malignancy, including extreme anisocytosis, anisokaryosis, and bizarre mitotic figures. Large round granular pink intracytoplasmic inclusions are often noted in occasional cells, however these are not unique to this tumor, nor is the precise nature of their composition characterized (Fig. 9). Transitional cell carcinomas can also involve the kidney and ureter as well as the urinary bladder. Reports of tumor seeding of the needle track subsequent to transabdominal aspiration indicate that traumatic catheterization is the preferred method for sample collection,[13] however some clinicians feel that the presentation of animals in the late stages of disease limits the clinical significance of this uncommon complication. Seeding can also occur during surgical resection. Metastatic neoplasia can also be identified in the kidney by cytology; however, definitive identification of the tissue of origin cannot always be established.

Endocrine Tissues

Cytologic evaluation of endocrine tissues in animals is predominantly performed in dogs and cats to evaluate for the presence or absence of neoplasia. Cytologically, most endocrine neoplasms in veterinary medicine manifest a similar, so-called "neuroendocrine" appearance, which classically presents as a uniform, biologically indolent appearing population of fragile cells with round nuclei in which broken cells (often termed naked nuclei) often predominate.

As in people, cytologic sampling of the thyroid is diagnostically important, and is followed, in frequency of sampling, by the adrenal gland, and the endocrine pancreas. Cytologically, canine and feline thyroid tumors are almost identical, both manifesting a classical neuroendocrine appearance, namely a sample composed of fragile and frequently disrupted cuboidal epithelial cells with a moderate amount of light basophilic cytoplasm and indistinct cell margins. There is usually a single centrally placed round to oval nucleus with minimal atypia. Amorphous eosinophilic colloid is often observed (Fig. 10). Despite similar cytologic findings, the biological behavior of canine and feline thyroid tumors are radically different, with the vast majority of canine tumors being invasive, metastatic, and nonfunctional while feline counterparts are almost always benign functional adenomas. Therefore, canine tumors are always presumed to be malignant, however, cytology is performed to distinguish thyroid origin lesions from other potential neoplastic and inflammatory lesions that occur in the neck region and throughout the

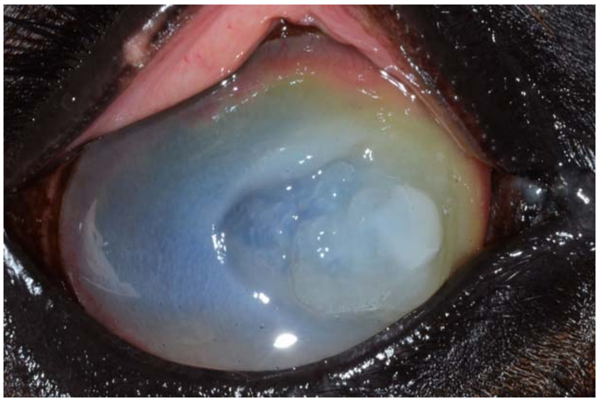

Fig. 11. Keratomycosis. Horse. Gross image of eye. Melting corneal ulcer due to keratomycosis (See Fig. 12). Image courtesy of Dr. Michala De Lind Henriksen. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

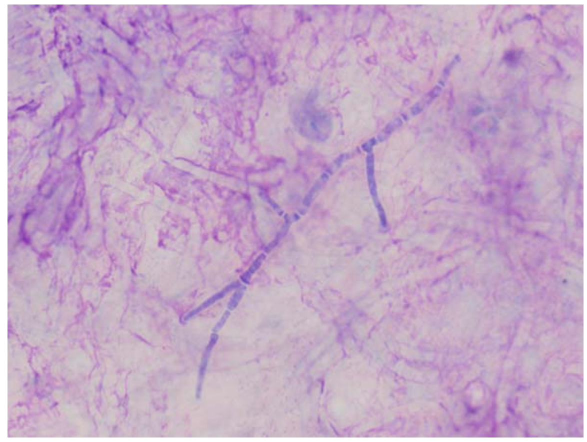

Fig. 12. Keratomycosis. Horse. Corneal swab collected from the eye lesion depicted in Figure 11. Basophilic, septate, branching, fungal hyphae. Nonstaining fungal hyphae can also be seen (Wright–Giemsa, ×500). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

thoracic cavity due to the frequency of potentially neoplastic ectopic thyroid tissue in the dog.[14,15]

Cytology is occasionally used to evaluate adrenal masses in dogs. Pheochromocytomas, like other endocrine neoplasms, have a classical neuroendocrine appearance. Adrenocortical tumors are relatively common in dogs and ferrets. In both species, the tumors are usually functional and can be benign or malignant, with benign tumors indistinguishable from hyperplasia and overlap in the cytologic appearance between adenomas and well-differentiated carcinomas. Ultrasonographic evidence of ≥5 cm major axis length, metastatic disease, or thrombosis predict poor prognosis when histologic confirmation of malignancy is not feasible.[16] Adrenal cortical tumors of dogs are very similar to people and serve as an animal model for human disease, although levels of hormone secretion are significantly higher in dogs.[17] The disease in ferrets is slightly different, often the result of early neutering leading to the accumulation of neoplastic cells that secrete sex steroid and resemble steroidogenic cells of gonadal origin.[17] The syndrome is so classic that cytology of the adrenal glands in ferrets is often not performed.

Insulinoma of the exocrine pancreas is relatively common in the ferret, occasionally seen in dogs, but is rare in cats. Intermittent periods of symptomatic hypoglycemia in the absence of liver disease usually prompts imaging of the abdomen to evaluate animals for insulinoma or other malignancies that may produce similar clinical signs due to production of insulin-like growth factors. Although many insulinomas in ferrets are too small to detect by imaging, lesions can be visualized in dogs for the collection of cytologic samples, which can be diagnostic in combination with other clinical information.[18] Insulinoma cells have a generic neuroendocrine appearance similar to thyroid follicular cells; like thyroid tumors, cytologic atypia is a poor indicator of biological behavior and most insulinomas have aggressive biological behavior with estimates that most tumors have already metastasized by diagnosis.[18]

Ocular

Virtually all components of the globe and orbit can be cytologically sampled in all species; however the conjunctiva and cornea are the most frequent. Normal cytology of the dog and horse conjunctiva is composed primarily of sheets of superficial, intermediate, and basal epithelium.[19,20] Conjunctival cytology can be used to detect hyperplasia associated with keratoconjunctivitis sicca, which results in large numbers of keratinized squamous cells and can be used to classify the inflammatory infiltrate, and sometimes reveal etiologic agents, in infectious conjunctivitis. Like HSV-1 in people,[21] feline herpesvirus (FHV-1) is a major cause of acute and chronic keratoconjunctivitis in cats and can be cytologically characterized by eosinophilic inflammation, multinucleated epithelial cells, and intranuclear inclusion bodies, however for definitive diagnosis, PCR has better sensitivity.[22] Likewise, characteristic intracytoplasmic inclusions in the epithelial cells of canine conjunctival samples can support a diagnosis of distemper virus infection, which unfortunately has the potential to infect a wide spectrum of wild carnivores, including endangered species exposed to domestic dogs.[23] In horses, infection with nematode larvae of *Habronema muscae, Habronema majus,* or *Draschia megastoma* causes habronemiasis, a proliferative, ulcerative, and presumably hypersensitivity-mediated lesion of the eye and surrounding skin.[24] Cytologic findings include eosinophilic and mastocytic inflammation, however organisms may not be demonstrated and histopathology may be required to confirm the diagnosis.

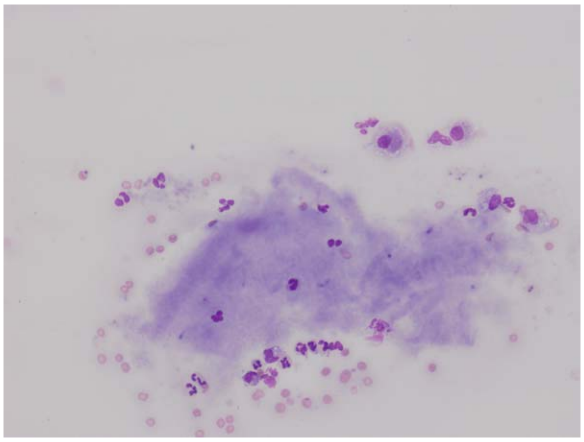

Fig. 13. Bile peritonitis. Dog. Abdominal fluid. Amorphous basophilic material consistent with mucinous or "white" bile. Neutrophils and large mononuclear cells are admixed with this material (Wright–Giemsa, ×200). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Corneal cytology is most useful in the diagnosis of infectious/inflammatory and, less commonly, neoplastic disease. Cytology samples from the normal cornea consist of non-keratinized squamous epithelial cells and cytologic evidence of keratitis can be seen as a result of infection with a similar spectrum of bacterial and viral etiologies as described for the conjunctiva. Unique to horses is a syndrome of idiopathic eosinophilic keratitis that is responsive to systemic immunosuppression.[25] Keratomycosis is of particular importance in horses, which are presumably predisposed because of the exposed position of the equine eye, instability of the tear film, and ubiquitous presence of fungal organisms in their environment.[26] Cytology is a standard part of the diagnostic process for suspected cases of equine keratomycosis and samples are characterized by a mixture of epithelial cells, many non-degenerate neutrophils, and fungal elements, most commonly *Aspergillus spp., Fusarium, spp, and Candida spp* (Figs. 11 and 12). Although in many cases organisms will be quite numerous, the sensitivity of cytology can be impacted by the predilection of organisms to grow deep into tissues, resulting in false negative cytology results. For this reason, culture and sometimes histopathology are also commonly performed. Although corneal neoplasia is rare, squamous cell carcinoma is among the most commonly observed.

While the iris, ciliary body, aqueous humor, and vitreous body can all be evaluated cytologically, they are less frequently evaluated than the conjunctiva and cornea. Blastomycosis, particularly in the Upper Midwest, and lymphoma are the most common causes of infectious and neoplastic uveitis, respectively, and both are amenable to cytologic diagnosis.[27] One small study suggests that the sensitivity of aqueous humor cytology for the detection of neoplasia may be slightly higher in dogs than cats.[28]

Central Nervous System

Although the central nervous system (CNS) is an uncommon cytologic source in veterinary medicine, samples from the CNS are often diagnostically useful, as illustrated by three studies demonstrating complete to near-complete agreement with histopathology in 80–100% of cases.[29–31] These findings mimic comparable human neurosurgery studies, where cytology has emerged as the preferred diagnostic tool compared to frozen-section histopathology.[32–34] Focal CNS disease, which is most commonly the result of neoplastic or inflammatory disease, is most amenable to cytologic examination.[35] In dogs and cats, meningioma is the most common primary brain tumor, representing 45% and 85% of cases of primary intracranial neoplasia.[36–38] Cytologically, meningioma is characterized by the presence of whorl formations of epithelial- or mesenchymal-appearing cells.[39] Of note, owing to shared clinical and genetic features, there is increasing evidence for the usage of the dog as a natural model for gliomas, which are the most common primary brain tumor in humans and the second most common in dogs.[40,41] In addition to neoplasia, cytology of the CNS can be used to identify focal inflammatory lesions, most notably of fungal origin. With the possible exception of cryptococcosis, fungal infections of the CNS are uncommon in veterinary medicine. Cryptococcus is the most common fungal disease in cats and has a predilection for the CNS in both dogs and cats.[41–43] CNS involvement with other fungal organisms is uncommon, although there are reports of brain and spinal cord infections in blastomycosis, histoplasmosis, coccidiomycosis, phaeohyphomycosis, aspergillosis, and fusariosis.[41]

Fluid Analysis

Analysis of body fluids is commonly performed in veterinary species. Abdominal and pleural fluids are most commonly submitted and thus will be the focus of this review, however synovial, cerebrospinal, and pericardial fluid analyses are also performed, particularly in referral practice settings. In healthy animals, there is very little fluid in the pleural space and abdominal cavity, with the exception of large animal species (e.g., the horse and cow), in which abdominal fluid can be readily collected from normal animals. Normal cavity fluids have very low protein content ($\leq$2.5 g dl^{-1}), as well as low nucleated cell counts. In dogs and cats, nucleated cells should be <1,000 cells μl^{-1}, however fluid from healthy horses can have up to 10,000 cells μl^{-1}. Cytologically, mononuclear cells (mesotheial cells, lymphocytes, and mononuclear phagocytes) predominate in normal small animal body cavity fluid. In contrast, normal body cavity fluid in the horse can demonstrate more variability in nucleated cell differential, which can vary from mononuclear cell dominated to neutrophil dominated. Automated methods for cell counting have replaced manual ones, although microscopic differential cell counts remain the standard of care.[44]

Categorization of effusions in veterinary medicine follows the transudate, modified transudate, and exudate scheme with similar specific categories (i.e., chylous, neoplastic, hemorrhagic, bilious, etc).[45] Sterile inflammatory exudates can be associated with pancreatitis in small animals, uroperitoneum, and bile peritonitis, the latter of which is most commonly seen in dogs. Cytologic evidence of bile is typically evident by the presence of yellow to green or blue/black pigment, however the presence of amorphous-to-fibrillar, basophilic mucinous material similar to "white bile" described in people can also be found in certain cases of canine bile peritonitis (Fig. 13).[46] Horses do not have gall bladders, limiting the significance of this condition in those species. Hemorrhagic effusions may be seen in cases of trauma or coagulopathy, although in older dogs, particularly those of predisposed breeds (e.g., German shepherds, golden retrievers, and boxers), ruptured hemangiosarcoma of the spleen or liver is considered an important differential diagnosis. Feline infectious peritonitis is a lethal immune-mediated disease associated with infection with a feline coronavirus.[47] The "wet" or effusive form of the disease results in very high protein (>8.0 g dL^{-1}), straw-to-golden colored, hazy abdominal or thoracic effusion with moderate numbers of nucleated cells of inconsistent distribution.[47] In horses, abdominocentesis and cytologic fluid analysis are routinely performed as part of the diagnostic evaluation for any gastrointestinal disease (often generically referred to as "colic"). Septic inflammation may be associated with rupture of the gastrointestinal tract, although in peracute cases, which may lack significant inflammation, cytologic distinction from inadvertent enterocentesis is vital.

The most frequent neoplasms diagnosed cytologically during fluid analysis are lymphoma and carcinoma. As noted above, flow cytometry and molecular diagnostics can be of value in low cellularity samples or when cytologic features are not compellingly diagnostic. Carcinomatosis can be difficult to distinguish from severe reactive mesothelial hyperplasia because of overlap in the degree of cytologic atypia.[45] Mesothelioma has been reported in dogs, cats, and horses, but is rare and often cannot be reliably cytologically distinguished from carcinoma or severe mesothelial hyperplasia. Cytologically, owing to their morphologic overlap, it is often impossible to identify a tissue or origin (primary or metastatic) of a carcinoma cell population in a peritoneal or pleural fluid sample, with the potential exception of gastric squamous cell carcinoma (SCC) in horses. Gastric SCC is the most common stomach tumor in horses and can exfoliate neoplastic squamous cells into cavity effusions through metastasis or erosion through the gastric wall.[48]

Conclusion

This brief survey of veterinary diagnostic cytology demonstrates that veterinary and human cytology have many similarities, as well as some important differences. Ancillary testing in veterinary cytology is more limited in scope, but growing rapidly, especially in the most common companion animal species. The breadth of species in veterinary medicine is reflected in important differences in basic anatomy and physiology, disease prevalence, and the biological behavior of infectious diseases and neoplasms that must be considered by the veterinary cytologist. Advances in human cytology lay groundwork on which veterinary cytology may build; likewise, animal diseases can provide valuable translational models for human conditions.

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