ORIGINAL RESEARCH

Diagnostic accuracy of brush cytology in canine chronic intranasal disease

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Background: Most cases of canine chronic intranasal disease cannot be differentiated based on clinical examination alone, and biopsy is often required for a definitive diagnosis. Nonsurgical cytologic and histologic biopsy techniques represent desirable diagnostic approaches.
Objective: The aim of this retrospective study was to determine the diagnostic accuracy of brush cytology in differentiating non-neoplastic and neoplastic diseases in dogs with chronic intranasal disease.
Methods: Cytologic samples of lesions in dogs with chronic intranasal disease were obtained by brushing over a 12-year period. All dogs had complete physical examinations as well as radiographic, rhinoscopic, and cytologic evaluation. Histologic diagnosis, follow-up clinical information, or both were used as the gold standard, and dogs free of disease or with no progression of disease at 1 year were considered negative for neoplasia. Indicators of performance of brush cytology in detecting neoplasia were calculated and included sensitivity, specificity, positive and negative likelihood ratios, and diagnostic odds ratio.
Results: Samples of nasal brushings from 138 dogs were evaluated. Of 62 cases of neoplastic disease, true-positive and false-negative diagnoses were made using cytologic evaluation in 44 (71.0%) and 18 (29.0%) cases, respectively. False-negative diagnoses of neoplasia were not attributed to low cellularity, but to the presence of inflammatory cells that masked neoplastic cells. Brush cytology had a sensitivity of 0.71, specificity of 0.99, positive likelihood ratio of 53.94, negative likelihood ratio of 0.29, and diagnostic odds ratio of 188.33.
Conclusions: Brush cytology has good diagnostic accuracy for chronic intranasal lesions in dogs.

Introduction

Chronic intranasal disease in dogs is a relatively frequent cause of clinical complaint and often represents a diagnostic challenge. The nasal cavity tends to react to stimuli in a limited number of ways, regardless of the cause, and therefore clinical signs as a rule, are nonspecific. Imaging studies, such as radiographic or computed tomographic examination, or rhinoscopy are commonly used as diagnostic tools in the diagnosis of chronic intranasal diseases. However, a definitive diagnosis often depends on histologic examination of an adequate biopsy sample.[1–5] Although biopsy material is best obtained by rhinotomy, a number of nonsurgical techniques, blinded or endoscopically guided, have been used for collecting samples for both cytologic and histologic examination. For cytologic examination, direct smears of nasal discharge or material collected on swabs or by flushing, aspiration, brushing, imprints and squash preparations can also be prepared.[3,4,6–12] Samples for histologic examination can be obtained by flushing,[3,12] punch biopsy, use of a catheter,[2,5] and rhinoscopy-assisted pinch biopsy.[1,6,8,9]

The skill of the individual collecting the sample, type of procedure used, distribution of the lesion (eg, focal to diffuse; superficial or deep), exfoliative capacity of the lesion, and presence of an inflammatory process or necrosis are factors that may influence success of obtaining a diagnostic sample. Methods that permit collection of representative deep mucosal samples are preferred. However, the main obstacle to obtaining a diagnostic sample is the difficulty in visualizing the nasal cavity during sampling. In general, advanced imaging techniques that aid in the identification of occult masses increase diagnostic potential. Studies of cytology of intranasal disease using different techniques have been reported[3,4,6–9]; the best diagnostic rates were reported for 30 cats with nasopharyngeal masses using squash preparations (90%)[9] and for 85 cats with chronic intranasal disease using brush cytology (86.8%).[6]

The objective of this retrospective study was to determine the diagnostic accuracy of brush cytology in differentiating non-neoplastic and neoplastic disease in dogs with chronic intranasal disease with histologic diagnosis, follow-up clinical information, or both used as the gold standard.

Materials and Methods

Inclusion criteria

For this retrospective study, a database of samples submitted to the Department of Veterinary Pathology at the University of Milan from January 1992 to December 2004 was searched for samples collected using brush cytology from dogs presented to the Department of Veterinary Clinical Sciences for chronic intranasal disease. Medical records were retrieved to obtain historic data and clinical findings, and diagnostic procedures were performed. Guidelines that comprise the Standard for Reporting of Diagnostic Accuracy (STARD) were followed.[13,14]

Dogs with nasal signs that were recurrent or had been present for at least 2 months and for which cytologic samples had been collected by brushing were included. To assess the diagnostic accuracy of brushing, the cytologic diagnosis was compared with the histologic diagnosis, follow-up clinical findings, or both. In cases of cytologic diagnoses of non-neoplastic lesions, even those confirmed using histologic examination, a follow-up examination at 1 year was required to consider the dog negative for nasal neoplasia. In cases of cytologic diagnoses of neoplasia, histologic confirmation or follow-up evaluation supporting the neoplastic origin of the nasal disease, based on progression of the lesion, was required.

Sample collection and processing

All dogs received a complete physical examination with thorough inspection of the nasal cavity, including radiographic examination of the skull, nasal cavity, and frontal sinuses; rhinoscopic examination with a flexible fiberoptic videobronchoscope, the Fujinon EB-250s with a diameter of 4.8 mm and a length of 80 cm (Fuji Photo Optical Co. Ltd., Saitama, Japan); and collection of samples for cytologic examination using the brush technique. This technique entailed the use of a small cylindrical nylon brush that was inserted into the nasal cavity with endoscopic guidance. The brush was rotated as it was moved back and forth over the lesion,[10] and the harvested material was then gently spread on glass slides. The sampling procedure was repeated until the amount and appearance of material, based on gross visualization, were considered adequate for submission for cytologic evaluation. Slides were air-dried and stained with routine Romanowsky-type stains: Hemacolor (Merck KGaA, Darmstadt, Germany) and/or May-Grünwald Giemsa (Merck KGaA, Frankfurt, Germany).

Samples for histologic examination were obtained either using endoscopic pinch biopsy or excisional biopsy or at necropsy. Samples obtained using endoscopy were taken at the same time as brushing was performed. Samples obtained by excision or at necropsy were always taken within 15 days of obtaining the brushing, as differences in when samples are collected for cytologic and histologic examination may affect the results.[14] Tissue samples were fixed in 10% neutral buffered formalin, processed routinely, and embedded in paraffin wax. Sections of 5 μm were stained with H&E.

Cytologic evaluation

Reports of the cytologic examination in the database were prepared by diplomates of the European College of Veterinary Pathologists (MC) or European College of Veterinary Clinical Pathologists (GG) or 1 board-eligible clinical pathologist (NPdC). For the purpose of the study, the diplomates reviewed all cases. The cytopathologists were blinded to signalment, history, clinical data, and histologic diagnosis when evaluating and interpreting the cytologic samples.

Cellularity of cytologic samples was assessed on low power magnification (10x objective lens) and ranked on a scale of 0–3, with 0 = inadequate,

1 = low, 2 = moderate, and 3 = good. Lesions were first categorized as neoplastic or non-neoplastic. In the case of neoplasia, cell type and malignancy were determined according to standard criteria.[15] Inflammation, hyperplasia, and metaplasia were included in the non-neoplastic category. Inflammatory processes were further categorized based on the predominant cell type, and the sample was evaluated for the presence of etiologic agents. Similar to other studies,[14,16–18] our analysis only included the primary pathologic process. Thus, samples with mixed processes that included neoplastic cells were simply classified as neoplastic.

Histologic evaluation

Reports of the histologic examination were prepared by a diplomate of the European College of Veterinary Pathologists (GA) who was blinded to the cytologic diagnosis. Neoplasms were diagnosed according to the World Health Organization's histologic classification of tumors in domestic animals.[19]

Follow-up

Follow-up information was obtained both by personal visit (SR, CMM) and telephone contact (SR, CMM, GG). Dogs free of disease or without disease progression 1 year after brush sampling were considered negative for neoplasia.

Indicators of diagnostic performance and statistical analysis

The diagnostic accuracy of cytologic evaluation of brush for neoplastic and non-neoplastic intranasal lesions in dogs was calculated. Point and interval (95% confidence interval) estimates of sensitivity, specificity, positive and negative likelihood ratios, and diagnostic odds ratio were calculated using a 2×2 table. Confidence intervals for positive and negative likelihood ratios were based on formulae previously desribed.[20] Estimates of sensitivity and specificity of brush cytology, correlated with the cellularity of the sample, were calculated.[21–23] Samples for which inadequate cellularity or poor smear or stain quality precluded a cytologic diagnosis were considered inadequate, and were excluded from statistical analysis. All statistical analyses were performed using R statistical software (R Development Core Team, Wien, Austria).[24] Methods for calculating test reproducibility were not addressed by this study design.

Results

In the database search, 171 dogs with chronic intranasal disease were identified; of these, 33 were excluded owing to lack of histologic diagnosis or follow-up information (27 cases) or to inadequacy of the sample (6 cases). Of the latter, inadequacy was due to poor cellularity with abundant blood contamination in 2 cases (1 sarcoma, 1 adenocarcinoma) and to poor quality of slide preparation and staining in 4 cases (1 adenocarcinoma and 3 chronic inflammatory processes). The final study included 138 cases with an overall retrieval rate of 80.7% (138/171) for cytologic samples and with exclusion of 3.6% (6/171) inadequate samples. Adverse events were not recorded in any of the 138 medical records.

The mean age (range) of the dogs was 7.9 years (1–16 years). There were 85 males (55 neutered) and 53 females (44 spayed). Breeds included mixed breed (33), German Shepherd (23), English Setter (9), Siberian Husky (7), Boxer (5), Schnauzer (5), Yorkshire Terrier (5), Doberman (4), Miniature Poodle (4), Samoyed (3), Belgian Sheepdog (3), Fox Terrier (3) Golden Retriever (2), Alaskan Malamute (2), German Drahthaar (German Wirehaired Pointer, 2), Dachshund (2), Maremma Sheepdog (2), and Rottweiler (2). Nineteen other breeds were represented by 1 dog each.

The cytologic diagnosis of neoplastic or non-neoplastic disease agreed with the histologic diagnosis in 119 of 138 (86.2%) cases (Table 1). Brush cytology had high specificity and a high positive likelihood ratio for the diagnosis of neoplasia (Table 2). Cytologic samples with high cellularity had lower sensitivity for a diagnosis of neoplasia compared with samples having low or moderate cellularity (Table 3).

In 93 of the 138 cases (67%), cytology brush samples were classified as non-neoplastic, and 18 of these were false negatives for neoplastic disease. True negatives (TN) comprised 75 of 76 cases (98.7%) as the cytologic diagnosis of non-neoplastic disease was in agreement with histologic diagnosis and 1-year follow-up (n = 31 cases: 28 pinch biopsies, 1 case with both pinch and surgical biopsies, 2 surgical biopsies) or with 1-year follow-up alone (n = 44 cases: 30 cases by personal visit, 14 cases by telephone conversation). Of these 75 cases, 67 had an inflammatory process and 8 had variable features of increased numbers of goblet cells, abundant mucus, hyperplastic, dysplastic, or metaplastic respiratory epithelium, and absence of a significant inflammatory component and were simply categorized as non-neoplastic. In 19 of 67 cases of inflammation, a nonbacterial etiologic agent was identified with 9 cases each of aspergillosis and

Table 1. Comparison of diagnoses of neoplasia made by cytologic examination or by histologic examination/follow-up evaluation of nasal lesions in 138 dogs.

Neoplasia Diagnosed by Cytologic Examination	Neoplasia Diagnosed by Histologic Examination or Follow-Up Evaluation	
	Positive	Negative
Positive	44	1
Negative	18	75
Total	62	76

Table 2. Estimates of the diagnostic accuracy of diagnosis of chronic intranasal disease in 138 dogs based on cytologic examination of brushings.

Parameter	Estimation	Range	Confidence Interval
Sensitivity	0.71	0.58–0.82	95%
Specificity	0.99	0.93–1.00	95%
Positive likelihood ratio	53.94	7.65–380.43	95%
Negative likelihood ratio	0.29	0.20–0.43	95%
Diagnostic odds ratio	183.33	23.65–1420.96	95%

rhinosporidiosis with neutrophilic inflammation, and 1 case of leishmaniosis with mixed macrophagic and lymphocytic inflammation. In the remaining cases, inflammation was classified as neutrophilic in 23 of 67, of which 5 had evidence of bacterial phagocytosis, and as mixed in 25 of 67. In 28 cases of inflammatory disease in which both cytologic and histologic evaluations were available, the type of inflammatory cells matched in 23 cases (82%). In the other 5 cases (18%), cytologic examination showed superficial neutrophilic inflammation ($n = 2$), hyperplastic epithelial changes ($n = 2$), or eosinophilic inflammation ($n = 1$), but failed to demonstrate the deeper lymphoplasmacytic infiltrate that was evident on histologic examination.

In 18 of the 93 cases (19.4%) with a cytologic diagnosis of non-neoplastic disease, the diagnosis constituted a false negative (FN) (Table 4); the histologic diagnoses, made by evaluation of 15 pinch biopsies, 2 cases with both pinch and surgical biopsies, and 1 surgical biopsy, included 12 epithelial cell tumors, 5 mesenchymal tumors, and 1 round cell tumor, and all tumors were malignant. Malignancy in one case was confirmed by examination of the surgical biopsy sample, whereas the pinch biopsy sample was negative for neoplasia.

In 45 of the 138 cases (33%), cytology brush samples were classified as neoplastic (Table 5). In 41 of these 45 cases, the diagnoses were confirmed by histologic examination of 31 pinch biopsies, 8 cases with both pinch and surgical biopsies, 1 surgical biopsy, and 1 sample obtained at necropsy, and were considered true positives (TP). Malignancy in 2 cases was confirmed by examination of the surgical biopsy sample, whereas the pinch biopsy sample was negative for neoplasia. In 3 of the 45 cases diagnosed as neoplasia (2 carcinomas and 1 sarcoma) by cytologic examination, neoplasia was not evident by histologic examination of a pinch endoscopic biopsy sample. However, follow-up evaluation, obtained by a personal visit, supported the neoplastic origin of the disease, as the lesions had rapidly progressed based on size and local extension. Consequently, these cases were considered as TPs. In 1 of the 76 cases of non-neoplastic disease, a false-positive (FP) cytologic diagnosis of mast cell tumor was made based on the finding of moderate numbers of well-granulated mast cells with some clustering of cells (Figure 1). The histologic diagnosis, made on examination of an endoscopic pinch biopsy sample, was eosinophilic granuloma. The dog was a Siberian husky and was not treated either surgically or with chemotherapy. A follow-up visit and telephone conversation 6 years later confirmed the non-neoplastic origin of the disease.

Of 62 cases of intranasal tumors diagnosed by histologic examination and follow-up evaluation or by follow-up evaluation alone, 44 TPs (70.1%) were identified by cytologic examination. Considering tumor type, brush cytology was accurate for the diagnosis of

Table 3. Estimates of sensitivity and specificity of brush cytology correlated with cellularity of the sample.

Cellularity	Cytologic Diagnosis of Neoplasia	Neoplasia		Sensitivity	Specificity
		Positive	Negative		
Low	Positive	15	1	83.3 (58.6–96.4)	96.1 (80.4–99.9)
	Negative	3	25		
Moderate	Positive	17	0	85.0 (62.1–96.8)	100 (83.2–100)
	Negative	3	30		
Good	Positive	12	0	50.0 (29.1–70.9)	100 (76.1–100)
	Negative	12	20		

Table 4. False-negative cytologic diagnoses for malignant nasal tumors in 18 dogs.

Signalment	Main Cytologic Findings	Additional Cytologic Findings	Histologic Diagnsois
Mixed, M, 14 years	Neutrophilic inflammation	Hyperplastic epithelium	Adenocarcinoma
Samoyed, F, 4 years	Neutrophilic inflammation	Hyperplastic epithelium	Adenocarcinoma
Setter, M, 14 years	Mixed inflammation	Necrosis	Adenocarcinoma
Mixed, F, 9 years	Mixed inflammation	Mast cells, mucus	Adenocarcinoma
Irish Setter, M, 9 years	Mixed inflammation	None	Adenocarcinoma
Mixed, M, 7 years	Neutrophilic inflammation	None	Transitional carcinoma
Mixed, F, 13 years	Neutrophilic inflammation	None	Transitional carcinoma
German Shepherd, M, 6 years	Neutrophilic inflammation	Bacterial phagocytosis, hyperplastic epithelium	Transitional carcinoma
Mixed, M, 5 years	Neutrophilic inflammation	Necrosis	Transitional carcinoma
Fox Terrier, M, 8 years	Epithelial hyperplasia	None	Transitional carcinoma
Mixed, M, 14 years	Neutrophilic inflammation	None	Squamous cell carcinoma
Mixed, M, adult	Neutrophilic inflammation	Mycotic hyphae (PAS+)	Squamous cell carcinoma
Alaskan Malamute, M, 5 years	Neutrophilic inflammation	Rare spindle cells	Osteosarcoma
Mixed, M, 9 years	Neutrophilic inflammation	Bacterial phagocytosis, rare atypical spindle cells	Osteosarcoma
German Shepherd, F, 4 years	Neutrophilic inflammation	Bacterial phagocytosis	Chondrosarcoma
Belgian Shepherd, M, 10 years	Mixed inflammation	None	Sarcoma, NOS
Mixed, M, 7 years	Mixed inflammation	Osteoclasts, mast cells	Sarcoma, NOS
German Shepherd, M, 12 years	Neutrophilic inflammation	None	Round cell tumor, NOS

NOS indicates not otherwise specified.

Table 5. Comparison of cytologic and histologic diagnoses in 41 cases of neoplasia of the nasal cavity in dogs.

Cytologic Diagnosis	Histologic Diagnosis
Epithelial cells tumors (26)	
Carcinoma (23)	Adenocarcinoma (14)
	Transitional carcinoma (8)
Squamous cell carcinoma (3)	Squamous cell carcinoma (1)
	Squamous cell carcinoma (3)
Mesenchymal tumors (12)	Osteosarcoma (8)
	Chondrosarcoma (2)
	Hemangiosarcoma (1)
	Sarcoma NOS (1)
Round cell tumors (2)	
Transmissible Venereal Tumor (1)	Transmissible Venereal Tumor (1)
Lymphoma (1)	Lymphoma (1)
Melanoma (1)	Melanoma (1)

NOS indicates not otherwise specified.

28 of 40 (70.0%) epithelial neoplasms, 13 of 18 (72.2%) mesenchymal neoplasms, 2 of 3 (66.6%) round cell tumors, and 1 case of melanoma. Overall, the primary pathologic process was correctly diagnosed by cytologic evaluation as non-neoplastic or neoplastic in 119 of 138 cases (86.2%).

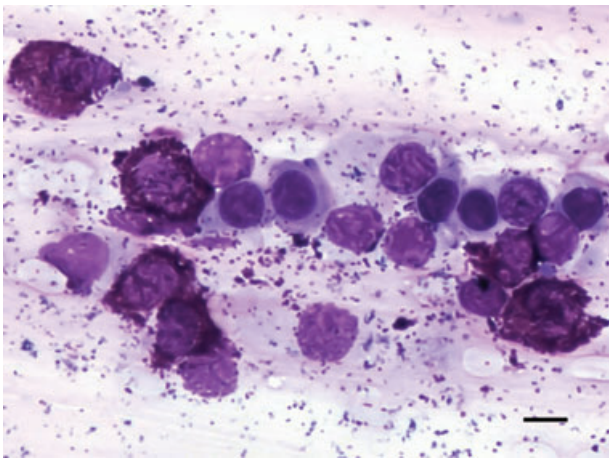

Figure 1. Cytologic sample of a nasal lesion obtained by brushing. Note moderate numbers of well-granulated mast cells, hyperplastic epithelial cells, and sparse mucus and granules in the background. This was the one false-positive result in this study: the cytologic diagnosis was mast cell tumor, but the histologic diagnosis, made on examination of an endoscopic pinch biopsy sample, was eosinophilic granuloma. May-Grünwald Giemsa, bar = 10 μm.

Discussion

Brush cytology was found to have good diagnostic accuracy for both neoplastic and non-neoplastic intranasal disease in dogs, and its use as an adequate screening test for chronic intranasal disease is supported by this large case study. The probability of a cytologic diagnosis of neoplasia being a true positive was about 54 times higher than the likelihood that it was a false-positive diagnosis. When a "negative" finding for neoplasia was obtained by cytologic examination, the probability of it being neoplasia (eg, a false negative) was 0.29 times lower than the probability that it was a "true negative." The overall probability that a case

would be correctly classified with a cytologic diagnosis was about 183 times higher than the probability of making a diagnostic error. Our results of 86.2% diagnostic accuracy parallel those of a similar study in cats.[6] In a study of 151 cases of intranasal brush cytology in humans, diagnostic accuracy was 91.4%.[25] These percentages cannot be strictly compared as accuracy may be affected by many variables, such as the proportion of neoplastic and non-neoplastic cases included, the type of non-neoplastic lesion, and the type and size of the neoplasm.

The correlations of sensitivity and specificity with cellularity of the sample were unexpected. Samples with good cellularity are often considered diagnostic, although in veterinary medicine, there is only one study, which evaluated diagnostic accuracy of bone cytology, that assessed the effect of cellularity and found a significant positive effect of cellularity on cytologic and histologic correlations.[14] In our study, specificity was not affected by the cellularity of the sample, and quality of the sample with evaluation of criteria of malignancy was more important than the quantity of cells. The one false-positive diagnosis of intranasal mast cell tumor, rarely reported in dogs,[26] was made without knowledge of endoscopic features, which were negative for neoplasia, and breed, in this case a Siberian Husky, a breed prone to developing eosinophilic granulomatous lesions with mast cells.[27,28] It should be emphasized that all clinical evidence should be considered in formulating a final cytologic diagnosis. Sensitivity, on the other hand, actually decreased with increasing cellularity and usually resulted from tumor-associated inflammation obscuring the neoplastic cells, a finding reported previously.[29] Neutrophilic inflammation is especially common in intranasal carcinomas in dogs.[30] In addition, in a study on persistent nasal diseases, it was demonstrated that multiple pathologic processes occurring simultaneously may cause erroneous cytologic interpretations.[31] In one false-negative case, the cytologic diagnosis was mycotic rhinitis, which, similar to bacterial rhinitis, may occur in the presence of an underlying lying neoplasm or other disorder.

One of the major limitations of diagnostic cytology is the presence of inadequate samples. Various nonsurgical approaches have been used in dogs to obtain cytologic or histologic samples of intranasal lesions, with most of the reports describing sampling of masses[1–5,7,8,12,32] For brush cytology, well-defined space-occupying intranasal lesions are not required and are often not present in cases of non-neoplastic lesions or in early stages of neoplasia. In this study, the number of inadequate samples was low. Other noninvasive techniques, such as intranasal flushing and swabbing,[3,12] have been abandoned, perhaps for technical reasons, particularly for flushing, and poor diagnostic yield.

Brush cytology was useful in the diagnosis of intranasal non-neoplastic conditions. As demonstrated for cats,[6] the presence of a deep mucosal lymphoplasmacytic infiltrate could not always be identified due to the superficial neutrophilic inflammation. The finding of bacteria in association with neutrophilic inflammation is not surprising and is probably due to the role of secondary infection with opportunistic bacteria. It is noteworthy that in about 25% of the non-neoplastic diseases diagnosed by cytologic evaluation in this study, an etiologic agent was found. The majority of these diagnoses were mycotic rhinitis, which is common in dogs.[8,32] About half the dogs were infected with *Rhinosporidium seeberi*, a microorganism with an aquatic habitat[33]; this outbreak in dogs occurred in northern Italy in mid-late 1990s after the Po river flooded the Po Valley (Pianura Padana) in 1994.[34,35] One dog in our study had intranasal leishmaniosis, which, although rare, has been described, occasionally in association with transmissible venereal tumor (TVT).[36–39]

Primary neoplasms of the nasal cavity are uncommon in dogs with an estimated population-based incidence of 81 per 100,000 dogs at risk[40] and 38 per 100,000 medical admissions.[41] The prevalence of primary sinonasal tumors has been calculated to be between 0.8% and 1% of canine tumors,[42] and the tumors usually are malignant and of epithelial origin.[43] Intranasal benign neoplastic lesions are difficult to diagnose by cytology, as demonstrated for both cats and dogs[6,7] and were not found in the current study, perhaps owing to their low prevalence.[44] For malignant neoplasia, the diagnostic accuracy of 70.1% using brush cytology in our study was higher than the 56% previously reported.[7] In another study based on fine-needle aspiration cytology, diagnostic accuracy for malignant neoplasia was 78.6%; however, the dogs in that study had advanced stages of neoplasia with evident facial deformity.[4] Although imprint cytology yielded 81% diagnostic accuracy for intranasal malignancy,[7] that technique uses biopsy samples, which are obtained by more invasive procedures[1,3,4,7,12] that may result in severe side effects, such as hemorrhage or even death.[12]

Regarding tumor type, we were able to diagnose carcinomas and sarcomas with similar diagnostic accuracy. Even though cells from mesenchymal tumors typically exfoliate poorly,[15] in our study, they often had more severe criteria of malignancy than did cells

from epithelial tumors, which may be difficult to differentiate from benign, hyperplastic, metaplastic, or dysplastic nasal epithelium if the tumor is well-differentiated. Our findings are in contrast to those previously reported for brush cytology in which diagnostic accuracy was 88% for carcinomas, but only 20% for sarcomas, for which exfoliation was poor.[7] Round cell tumors were rare in our study, consisting of one case each of lymphoma, which, as an intranasal tumor, occurs more frequently in cats[19] and TVT. The occurrence of TVT has been described in the nasal cavity of dogs,[45,46] and cytologic examination can be important to the diagnosis of this tumor, as it can be difficult on histologic examination to distinguish it from other round cell tumors, especially lymphoma, when it occurs outside the genital tract.[47] Finally, intranasal melanoma was identified in this study, and is uncommon, but has been previously reported.[48]

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