Cytology of Neoplasms that Occur on the Head and Neck
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I. Introduction

The purpose of this material is to provide information that may be useful in the identification of tumors associated with various structures on the head. A brief description of the cytologic appearance of specific tumors as well as biological behavior is provided.

II. Tumors of the Nasal Cavity

Intranasal tumors are more frequently encountered in the dog than in other domestic animals. Of these tumors, approximately 80% in the dog and 90% in the cat are malignant.

A. Epithelial tumors: Most of the nasal tumors seen are epithelial in origin. The most frequently encountered nasal tumors of epithelial origin are the carcinomas (squamous cell carcinoma, adenocarcinoma, and undifferentiated carcinoma). In the dog, 68% to 75% of the nasal tumors are adenocarcinomas whereas in the cat, squamous cell carcinomas are most frequently observed. Benign epithelial tumors (papilloma and adenoma) are less common.

1. The general cytologic features of epithelial tumors are that the cells exfoliate in clumps or sheets. They are very adherent to each other with extensive contact between adjacent cells, and clear zones between cells at areas of cytoplasmic junctions.

2. Epithelial cells have distinct cytoplasmic borders. Some cells may contain intracytoplasmic vacuolation, indicating a neoplasm of glandular origin, an adenoma or adenocarcinoma.

3. Nuclear characteristics are used to determine if a tumor is benign or malignant. Benign epithelial tumors (papillomas/adenomas) will have nuclei that are very uniform in size, shape, chromatin pattern, and nuclear to cytoplasmic ratio (N:C ratio). Malignant tumors (carcinomas/adenocarcinomas) have anaplastic features of anisokaryosis (variably sized nuclei), prominent multiple nucleoli, high and/or variable N:C ratio, clumped chromatin, and mitotic activity.

4. Squamous cell carcinomas have some distinguishing characteristics that help aid in the identification of this tumor. Unlike other epithelial tumors, cells from these tumors may be more individually arranged, with angular cytoplasmic borders. Most tumors are composed of anaplastic appearing squamous cells. The cells are usually very pleomorphic with variable N:C ratio. They contain moderate amounts of lightly basophilic to aqua-blue cytoplasm (keratinized). Some cells contain small, clear, punctate perinuclear vacuoles called keratohyalin granules. One prominent feature of squamous cell carcinomas is the presence of dysplasia and dyskeratosis, both of which indicate an abnormal cell development. Dysplasia is recognized when mature angular squamous cells, some with keratin or keratohyalin granules, contain immature nuclei. When keratin is being produced by cells with immature nuclei to a point where it is seen cytologically, sometimes compartmentalized in the cells, there is dyskeratosis (abnormal production of keratin). "Tadpole" like cells with eccentrically located nuclei and single blunted cytoplasmic tails are
occasionally seen. The nuclei are pleomorphic with coarse chromatin and prominent, multiple nucleoli. Well-differentiated SCCs may contain large numbers of fairly mature squamous epithelium.

5. **Biological behavior:** Most of the malignant epithelial tumors in the nasal cavity, including squamous cell carcinomas, tend to metastasize late in the course of the disease, but are locally very aggressive. Surgical resection is the preferred method of therapy, followed by radiotherapy if needed. Mean survival time with surgery alone or no treatment is 3 to 5 months for nasal tumors in general. Radiotherapy has significantly improved survival times with 38% - 57% of patients alive after 1 year and 30% - 48% of patients alive 2 years after treatment.

B. **Mesenchymal tumors:** Although less frequently encountered, benign mesenchymal tumors (fibromas), and malignant tumors (fibrosarcomas, chondrosarcomas, osteosarcomas, and rhabdomyosarcomas) may also be seen in the nasal cavity.

1. Cells from mesenchymal tumors in general exfoliate singularly, and contain wispy, spindle-shaped cytoplasm which trails off in one or two directions from the nucleus. The cytoplasmic borders of mesenchymal cells are often indistinct.

2. The nuclear features of malignancy are the same as for epithelial tumors.

3. **Chondrosarcomas and osteosarcomas** may be distinguished from other sarcomas by the presence of amorphous, eosinophilic, extracellular matrix (osteoid or chondroid), and the presence of multinucleated giant cells.

**Note:** Tumors involving mucosal surfaces (nasal cavity, gastrointestinal tract, respiratory tract, and urogenital tract) often become inflamed and infected. This can make the cytologic diagnosis of malignancy a challenge since inflammation can cause "reactive" changes in epithelial and mesenchymal cells that mimic malignancy.

4. **Biological behavior:** As with epithelial neoplasms of the nasal cavity, the prognosis for recovery with mesenchymal tumors is poor. In general, surgical resection, when possible, followed by radiotherapy is the recommended course of treatment.

C. **Round Cell Tumors:** Mast cell tumors, lymphoma and transmissible venereal tumors (TVT) are 3 round cell tumors that may be seen in the nasal cavity.

1. All round cell tumors are cytologically characterized by the presence of individual cells with round, distinct cytoplasmic borders.

2. **Mast cell tumors** of the nasal cavity are uncommon. However, when present in this location they are typically very aggressive and metastasize early during the course of the disease. This is regardless of the cytologic differentiation of the mast cells.

3. **Lymphomas** are composed of a predominant population of lymphoblasts with scant to moderate amounts of deeply basophilic cytoplasm. Nuclei are round to polygonal with a high N:C ratio.
4. **TVT** cells contain variable amounts of lightly to moderately basophilic cytoplasm which often contains small, punctate vacuoles. Nuclei are round to polygonal with coarse chromatin and 1 or 2 large prominent nucleoli.

5. **Biological behavior of TVT**: These neoplasms are considered malignant and require chemotherapeutic intervention. TVTs have the best prognosis for recovery due to the dramatic response to vincristine chemotherapy (0.5 mg/M² q7d for 6 - 10 weeks). Nasal lymphomas should be treated chemotherapeutically as are other lymphomas, with a protocol catered to the needs of the patient and desires of the client.

### III. Tumors of the Oral Cavity

Most oral neoplasms in the dog and cat are malignant. However, benign tumors are more commonly encountered in the dog.

#### A. Epithelial Tumors :

1. Benign epithelial tumors (oral papillomas) are frequently seen in the dog, but are uncommon in cats.
   a) Papillomas appear cytologically as normal squamous epithelium with variable amounts of stromal elements. In the dog, oral papillomas are usually seen in young animals (<1 year). They are usually multiple, and may spontaneously regress.

2. Malignant epithelial tumors are common in both species. The most common oral neoplasm in the cat being the **squamous cell carcinoma (SCC)**. In the oral cavity, they may be found on the palate, cheek, lip, gingiva, pharynx, tonsil, or tongue. SCCs most commonly occur on the rostral mandible. Their cytologic appearance has been described above under tumors of the nasal cavity.
   a) **Biological behavior**: The biological behavior of oral SCC is site dependent and aggressive. Tumors of the mandible are locally very aggressive, but slow to metastasize. SCC of the tonsils or caudal tongue are more likely to metastasize to lymph nodes and lungs, often by the time of diagnosis.

#### B. Mesenchymal Tumors :

1. *Benign mesenchymal tumors (oral epulides)* are frequently seen in the dog, but are uncommon in other species. There are **3 types of epulides**: fibromatous, ossifying and acanthomatous. Multiple epulides may be seen in cats.
   a) **Fibromatous epulides** are usually of low cellularity containing only a few benign-appearing spindle-shaped cells (stromal cells).
   b) **Ossifying epulides** contain spindle-shaped cells along with extracellular, amorphous, pink-staining osteoid. Most of the multiple epulides in cats are of the ossifying type.
c) **Acanthomatous epulides** (appears epithelial) contain low to moderate numbers of squamous epithelium in varying stages of development.

d) **Biological behavior:** Epulides are considered to be benign gingival proliferations, but some types may be invasive (acanthomatous epulis) causing severe bony lysis, and may recur after surgical removal. In one study, 11 of 13 epulides in cats were ossifying and 8 of those recurred following surgery (Vet. Pathol. 38:227-229, 2001). Surgery is the recommended therapy followed by radiotherapy if regrowth occurs.

2. **Malignant mesenchymal neoplasms** may also occur in the oral cavity, the most common of which is the **fibrosarcoma**. They may also appear on the palate, cheek, gingiva, or tongue. The most common locations for oral fibrosarcomas are the gingiva of the upper molars, the anterior mandible, and the palate.

   a) **Cytologic appearance:** Fibrosarcomas of the palate may appear the same as fibrosarcomas located elsewhere on the body. However, some may appear cytologically benign and may be misread as a fibroma. Exercise caution in making a cytologic interpretation of mesenchymal tumors involving the hard palate, particularly if bony lysis is involved.

   b) **Biological behavior:** Fibrosarcomas are locally invasive often resulting in bony lysis. Metastasis is rare.

C. **Melanocytic tumors:**

1. Melanomas are the most common oral neoplasm in the dog. They most frequently involve the gingiva or buccal mucosa (Vet. Pathol. 37:597-608, 2000). Chow Chows and Golden Retrievers were over-represented breeds. Most oral melanomas in the dog and cat are malignant.

2. **Cytologic appearance:** The cells may cytologically appear spindle-shaped, epithelioid, or a mixture of both. The cytoplasm often contains variable amounts of fine, brown-black to green-black pigment granules. About a of the oral melanomas lack obvious cytoplasmic pigment and are thus classified as amelanotic. However, cytologically small amounts of fine pigment can usually be found, even in poorly differentiated tumors. If cells from an aspirated lesion appear very anaplastic, and contain both mesenchymal and epithelial features, a malignant melanoma should be suspected.

3. **Biological behavior:** With cutaneous melanomas, the more pigmented tumors are more differentiated and less likely to behave aggressively. Most pigmented, cutaneous melanomas of the dog and gray horse are benign, and most well-differentiated, cutaneous melanomas are considered benign. However, oral melanomas, and melanomas involving the nail bed of the digits, are very aggressive. Even well differentiated (highly pigmented) tumors in these locations are aggressive and frequently metastasize to regional lymph nodes, usually by the time of diagnosis. The treatment of choice is wide surgical excision or amputation followed by chemotherapy if needed.
Melanomas are uncommon tumors in the cat, however, a recent study identified 5 types of cutaneous melanomas that occur in the feline: 1) epithelioid, 2) spindle, 3) mixed, 4) signet-ring, and 5) balloon cell.

a) The epithelioid, spindle-cell and mixed tumors of the cat are usually pigmented and often found on the ears, forehead, nose, and eyelids. Balloon cell and signet-ring types are typically amelanotic.

b) The balloon cell type is also usually found on the head. Cells are large and swollen with cytoplasm that appears like a balloon. The nuclei have many anaplastic features.

c) The signet-ring cell type is usually found on the shoulder, thorax, and flank areas. The cytoplasm is large and distended with the nucleus pushed off to one side, giving cells the signet ring appearance. The nuclei have many features of malignancy.

d) The signet-ring and balloon cell type are believed to be variants of the epithelioid cell type. They are highly aggressive with widespread metastasis. Mean survival time from surgical removal was 4.5 months.

D. Plasmacytoma: Extramedullary plasmacytomas are lymphoid neoplasms with site predilections for the skin (76%) of the digits and foreleg (32%) as well as the oral cavity (28%), ears, and gastrointestinal tract. This tumor more commonly affects dogs, however, there are reported cases in the cat. In the dog, there may be a breed predilection in Cocker Spaniels (11.1%), Boxers (9.4%), and Airedale Terriers (7.7%).

1. Cytologic appearance: Plasmacytomas have the cytologic appearance of other round cell tumors with aspirates yielding moderate to large numbers of individually arranged, round to oval cells with discrete cytoplasmic borders. These cells contain variable amounts of deeply basophilic cytoplasm. Many of the cells will have a characteristic "plasmacytoid" appearance with a round nucleus which is often eccentrically located in the cell. A perinuclear clear area "Golgi zone" is sometimes seen in the cytoplasm. There is moderate to marked anisokaryosis, and binucleation and multinucleation is occasionally observed.

2. Biological behavior: In the dog, these tumors are usually considered benign and surgical removal is curative in most cases. However, local tumor recurrence following incomplete surgical removal has been observed. In the cat, however, this neoplasm apparently has a much more aggressive behavior with frequent metastasis to regional lymph nodes, liver, and spleen. In this species, an associated monoclonal gammopathy is usually seen. In either species, plasmacytomas can, on occasion, be associated with local amyloid production, and rarely with amyloidosis or hypercalcemia.

IV. Miscellaneous Tumors of the Head

A. Basal Cell Tumors:

1. Basal cell tumors are common on the head and neck of the dog and cat, but rare in other domestic species. They are one of the most commonly reported cutaneous tumor
in the feline. They have also been called basal cell carcinomas, but since they are usually benign, this term does not accurately describe their biological behavior in domestic animals.

2. **Cytologic appearance**: Cytologically, these tumors contain tight clumps of epithelium with deep blue cytoplasm and high N:C ratio. Mitotic figures may occasionally be observed. There may be low numbers of mature sebaceous gland epithelium mixed within the clumps of basal cells. Sebaceous differentiation is associated with some basal cell tumors. Some basal cell tumors, especially in the cat, contain variable amounts of melanin pigment and must be distinguished from true melanocytic tumors. The cohesiveness of basal cells is a predominant differentiating feature. However, this distinction may at times be cytologically difficult since melanin pigment may be within the basal cells themselves.

3. **Biological behavior**: These tumors are slow growing and rarely metastasize. Surgical excision is usually curative, but recurrence may occur after incomplete excision.

**Note: Although some basal cells may cytologically appear anaplastic, this usually has no prognostic value in predicting the biological behavior.**

B. **Sebaceous Gland Tumors**:

1. Sebaceous gland tumors are cauliflower-like cutaneous lesions seen on the head (eyelids included) and trunk of dogs, and uncommonly in other species. Cocker spaniels, beagles, poodles, and basset hounds may be predisposed.

2. **Cytologic appearance**: Cytologically, sebaceous gland adenomas appear as clumps of epithelial cells with abundant, foamy, vacuolated cytoplasm. The N:C ratio is very low and nuclei are small and centrally to slightly eccentrically located. The cells of adenocarcinomas will be similar, but with a higher N:C ratio and many of the anaplastic nuclear features previously discussed.

3. **Biological behavior**: Most are benign (sebaceous gland adenomas); however, sebaceous gland adenocarcinomas may also be observed. Adenomas are benign and surgical resection is curative. Adenocarcinomas have a guarded prognosis and local recurrence of the tumor occurs in about 15% of the cases. Reports regarding metastasis with this tumor are contradictory.

C. **Salivary Gland Tumors**:

1. Primary neoplasms of the salivary glands are rare in domestic animals, but may be slightly more common in the cat than in the dog. Of tumors involving the major salivary glands, the parotid gland or submandibular gland are most commonly affected.

2. In the dog and cat, 75% to 85% of the salivary gland tumors are adenocarcinomas. Benign tumors consist of rare reports of adenomas (normal appearing glandular epithelium with very foamy, macrophage-like, cytoplasm) and mixed tumors (mixtures of epithelium, myoepithelium, myxoid/chondroid material, and bone).
3. Malignant tumors sometimes appear anaplastic containing nuclear and cytoplasmic features similar to other malignant epithelial tumors described above. However, some cytologists indicate well-differentiated carcinomas of the salivary gland may not be distinguishable from adenomas. Therefore, caution should be used in diagnosing a benign tumor of the salivary gland in the dog and cat, particularly since most salivary tumors are malignant. Salivary adenocarcinomas are aggressive, and metastasis to regional lymph nodes usually occurs early in the disease.

D. Ceruminous Gland Tumors:

1. The ceruminous glands are apocrine glands of the external ear canal. Tumors of these glands have been infrequently reported in domestic animals, most commonly the cat.

2. Benign (adenomas) or malignant (adenocarcinomas) may be seen; however, adenocarcinomas are more common. Adenomas are usually small and nodular, or pedunculated. They appear cytologically as well-differentiated epithelium with abundant vacuolated cytoplasm. Amorphous secretory material may be seen in the background. Adenomas must be differentiated from nodular hyperplasia of the ceruminous glands and chronic inflammatory polyps, which may occur secondary to chronic otitis.

3. Ceruminous gland adenocarcinomas appear cytologically as anaplastic secretory epithelium. Cytoplasmic vacuolation may be marked. Nuclear characteristics of malignancy such as variable N:C ratio, anisokaryosis, pleomorphism, prominent multiple nucleoli, and coarse chromatin are frequently observed. These tumors are usually aggressive, with metastasis occurring in about ½ of the cases. They may invade the parotid region and metastasize to regional lymph nodes and lungs. Prognosis is guarded.

E. Mast Cell Tumors:

1. Most cutaneous mast cell tumors in the cat (58%) are located on the head and neck.

2. The cytologic appearance and biological behavior of these neoplasms were previously discussed in the “Cytodiagnosis” section at the beginning of the material. More information is in the last section on “Criteria for Malignancy”.

V. Conclusion

A. Classify the lesion and if neoplastic, try to determine if benign or malignant.
B. Try to assess the tissue of origin as being epithelial, mesenchymal, or round cell.
C. Knowing the site predilection of certain neoplasms will aid in making a definitive diagnosis, which will provide more information regarding the biological behavior of the tumor as well as therapeutic and prognostic information.