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Feline Oral Neoplasia (8-Apr-2003)

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Introduction

Unfortunately, the vast majority of neoplasms found in the mouths of cats are malignant and carry a poor prognosis. Over 20 different types of cancer have been reported to occur in the oral cavity of felines, although only a few are observed commonly [1]. Among the more common feline oral neoplasms are squamous cell carcinoma (SCC), fibrosarcoma, lymphoma, and malignant melanoma. In fact, SCC alone accounts for about 70% of all feline oral tumors. It is of extreme importance to identify the tumor type and commence treatment early in the course of disease if a favorable treatment outcome is to be achieved. In the majority of cases, however, a clinical cure is not possible. Some oral tumors in cats are obvious, while others may present more subtly. Neoplasia must be suspected in all lesions of the feline oral cavity where an obvious cause is not clear. The first step towards treatment of feline oral neoplasia is establishing a correct diagnosis based on a biopsy.

When to Suspect Neoplasia

Any swelling (soft tissue or bony) or abnormal appearance of tissue in the oral cavity must be considered suspicious for neoplasia. In one study, however, it was shown that one-half of the swellings in the lower jaw bone of cats were non-neoplastic [2]. A common, but very subtle presentation of oral neoplasia is when a tooth is able to be extracted too easily. Whenever a tooth can be extracted with less-than-expected difficulty, the area surrounding the alveolus should be biopsied. Common presenting signs for cats with oral neoplasia include: an obvious oral mass, excessive salivation, weight loss, halitosis, bloody oral discharge, and dysphagia [3].

Obtaining a Biopsy

Obtaining a biopsy of a suspicious lesion in the oral cavity of the cat should be performed under general anesthesia maintained with a cuffed endotracheal tube. Prior to the anesthetic procedure, these cats should have undergone a workup minimally consisting of a physical examination, complete blood count (CBC), blood chemistry panel, urinalysis, and other ancillary procedures as indicated. If neoplasia is suspected prior to the procedure, a radiographic study (3-view chest radiographs) of the thoracic cavity to detect metastatic disease is also warranted.

With the cat under general anesthesia, the oral cavity should be thoroughly examined and all dental pathology recorded. At the time of biopsy, existing dental pathology should be addressed if possible. The area suspected of containing the neoplasm should be radiographed, ideally with intra-oral dental radiographs because of their superior detail [4].

The preferred method of obtaining a biopsy sample for oral lesions is an incisional biopsy [5]. An incisional biopsy is harvested from the interior of the lesion, leaving the suspected borders of the tumor behind. Make sure to procure a large enough sample to give the pathologist something to work with. In larger tumors, it is best to obtain multiple samples from different locations within the mass. Try not to take only the center of larger neoplasms, as this area may represent only a center of necrosis. It is also important to note that many tumors will have an overlying covering of hyperplastic epithelium. It is therefore important to make your biopsy deep enough to penetrate through this epithelial covering. Use a biopsy punch, scalpel blade or other sharp cutting device rather than electrocautery or laser, as the latter methods of excision tend to disturb cellular morphology. Once the biopsy sample is removed, the use of cautery or laser for hemostasis is not a problem.

If the biopsy results differ from your clinical impression, question the result [5]. The pathologist will benefit from coupling your description of the tumor's gross morphology and signalment/history with their histologic findings. It is not uncommon

for oral pathologists to change opinions on the nature of oral tumors - this is best done during the planning phase prior to extensive surgery.

Squamous Cell Carcinoma

Squamous cell carcinoma (SCC) is the most common tumor of the feline oral cavity. Approximately 60 - 70% of feline oral tumors are SCC [6]. The median age of cats with oral SCC is 11 - 13 years, however, cats as young as three years and as old as twenty-one years have been previously reported.

Feline oral SCC can have a variety of presentations. Most cases present with a mass in the mouth noted by the owner, however, others can present for halitosis, weight loss, dysphagia or ptosis. Importantly, some feline oral SCC lesions may have a true mass effect, whereas others can simply be erosive and/or erythematous. The presence of loose teeth in a cat should promptly alert the astute veterinary clinician to the possibility of bone lysis due to an underlying neoplastic process such as SCC.

The diagnostic workup for a cat with the suspicious diagnosis of oral SCC should be no different than that with any other pathologic process in the oral cavity. A thorough history, physical examination and oral examination should be performed with delineation of the process (i.e., size, location, color, firmness, does it cross midline, etc.) entered into the clinical record. A minimum database including bloodwork, urinalysis and retroviral testing should be performed if not done within the previous month. In addition, three view chest radiographs should be obtained for examination of pulmonary metastasis, and fine needle aspiration and cytology performed if any local lymph nodes are palpable, asymmetrical or enlarged. A recent publication in dogs and a small number of cats documents the potential clinical utility of performing aspirates of normally palpating lymph nodes [7]. It is presently unknown if this can be fully extrapolated to cats, but is likely true and these authors routinely perform aspirates of normal lymph nodes when neoplasia is suspected in the oral cavity of both dogs and cats. Lastly, an incisional biopsy should be performed with histopathologic examination. It is extremely important to note that the epithelium overlying some tumors can be hyperplastic, and therefore, the clinician must obtain deep incisional biopsies to allow the histopathologist to make the correct diagnosis. In addition, the simple submission of loose teeth for histopathological examination is routinely not sufficient for the confirmation of the diagnosis of oral SCC; procurement of the tissues deep to where the loose tooth was is strongly advised. The majority of cats will require a short general anesthesia for palpation of the area and detailed oral examination, local radiographs and biopsy. Occasional cases may also require the use of computed tomography scanning or magnetic resonance imaging to delineate the best treatment protocol and prognosis; this is especially true in those cases suspected to have caudal pharyngeal, orbital and/or nasal cavity tumor extension.

Feline oral SCC is an extremely invasive and malignant neoplasm. Unfortunately, to date, we have not found therapies, or combinations of therapies, that are substantially beneficial for feline oral SCC [1,6,8-11]. The recurrence rate for cats with oral SCC treated with surgery alone (and/or with radiation therapy) is felt to be extremely high with a median survival time less than 6 months [12], and these authors believe a median survival time of 30 - 60 days is more likely. The exception to this are cats with extremely small oral SCC involving the rostral mandible that may be able to undergo rostral mandibulectomy, however, it must be stated that even these cases can have recurrence in the face of histopathologically-determined "clean" margins. In addition, the use of radiation therapy as a sole treatment modality is also felt to be correlated with a median survival time less than six months, with a recent report documenting a median survival time of only 60 days with 3 large doses of palliative radiotherapy [13]. Though relatively few reports exist on the sole use of chemotherapy for feline oral SCC, it too is generally felt to be minimally beneficial when used in this way. In fact, these authors believe that the use of single modality therapy for feline oral SCC should be discouraged unless the tumor is a small rostral mandible SCC, or if the tumor is being palliatively treated with 3 - 6 large doses of radiation therapy.

The aforementioned lack of efficacy with single modality therapy in feline oral SCC suggests that multimodality therapy and/or novel therapies are necessary to make advances in the treatment of this aggressive cancer. Unfortunately, relatively few reports exist in the literature in this regard. These authors believe that "aggressive tumors must be treated aggressively" and therefore the future of feline oral SCC treatment lies in multimodality therapy, and a greater understanding of the molecular biology of this disease. Once the molecular alterations of feline oral SCC are determined, novel therapies may be able to be used that are more sensitive and specific than those presently being used. Though presently published only in abstract form, the use of regular fractionation radiation therapy and mitoxantrone by LaRue et al., has translated into a median survival time of ~6 months. At present, it is difficult to recommend aggressive multi-modality therapy in the face of such a poor prognosis, however, if the client is fully educated in regards to the prognosis, toxicity's and cost of the protocol, there is a subset of cats treated in this way with survival times greater than one year. This suggests that significant heterogeneity is present in feline oral SCC and that we still have much to learn about this devastating tumor.

A greater understanding of the biology (and specifically the molecular biology) of feline oral SCC may translate into improved treatment outcomes via the delineation of novel therapies. To this end, research is currently underway to investigate the molecular profile of this tumor. Head and neck SCC in humans appears to be a very similar condition to

feline oral SCC as both malignancies are extremely invasive, virulent and difficult to cure. Human head and neck SCC have mutated p53 (a potent tumor suppressor gene) as well as overexpression of a potent growth inducing protein (epidermal growth factor receptor; EGFR) [14]. Interestingly, feline oral SCC also have mutated p53 based on assays utilizing immunohistochemical overexpression of p53 [15]. In addition, preliminary work in the Flaherty Comparative Oncology Laboratory at the Animal Medical Center (PJB), suggests that most feline oral SCC over-express EGFR (data not shown and in progress). Novel anti-EGFR therapies are showing dramatic promise in human head and neck SCC experimental studies [16,17]. Since feline oral SCC appears to be a good clinical, and possibly a good molecular model for human head and neck SCC, we also may one day be able to take advantage of this exciting new therapy. Based on the general lack of success we have had to date with conventional therapies for feline oral SCC, we ardently look forward to the use of these rationally designed novel agents.

Fibrosarcoma

Fibrosarcoma (FSA) is the second most common tumor of the feline oral cavity. Approximately 10 - 20% of feline oral tumors are FSA [1,6]. FSA generally occurs in older cats (median age 10 - 12 years), however, cats as young as one year of age and as old as 22 years have been reported. There does not appear to be any gender predisposition or oral cavity site predilection, however, most cats with oral FSA have their tumors starting in the gingiva.

Other than the above descriptive data, there is extremely little clinical information on cats with oral FSA. Most cats with oral FSA will present for the same problems as cats with oral SCC, however, cats with oral FSA invariably will have a mass effect at the primary tumor site. The workup for the feline oral FSA patient is no different than that discussed above for oral SCC. Non-ulcerated oral FSA invariably has a significant amount of hyperplastic epithelium overlying the tumor, and therefore, procurement of a deep incisional biopsy is recommended to best ensure a correct histopathological diagnosis.

Feline oral FSA are extremely invasive malignancies necessitating wide surgical extirpation. Though few reports exist concerning recurrence rates with feline oral FSA, minimal surgical excision generally results in recurrence. Unfortunately, aggressive surgical extirpation of these tumors with histopathologically determined "clean" margins likely results in recurrence in 20 - 30% of cases due to their incredibly invasive phenotype. The routine use of radiation therapy in cats with large bulky oral FSA is generally discouraged. However, the use of radiation may be beneficial in cases with incomplete surgical resection for feline oral FSA, or if the radiation is being used palliatively (3 - 6 large doses). Similarly, the use of chemotherapy in this disease is generally discouraged due to the relative chemoresistance of soft-tissue sarcomas. However, chemotherapy is occasionally used in cats with large oral FSA in an attempt to downstage the tumor for later surgical resection, or in cats with high-grade (and therefore greater chance for metastasis) oral FSA.

Fortunately, like most soft tissue sarcomas independent of species of origin, feline oral FSA are not generally very metastatic. Less than 10% of feline oral FSA cases will have metastasis at the time of presentation. Therefore, this tumor is best treated with locally aggressive therapies. The vast majority of human, canine and feline soft tissue sarcomas that have had tumor grading schemes developed has demonstrated that this information is highly clinically prognostic [18,19]. Unfortunately, a tumor grading scheme for feline oral FSA has not been published to date, however, the astute clinician may be able to decipher a tumor grade "guesstimate" by reviewing the histopathology report for degree of differentiation/anaplasia, number of mitoses, as well as other parameters. If the tumor is growing slowly, has few mitoses and is well to moderately differentiated, this would likely represent a low-middle grade oral FSA and very likely portend an extremely low risk for the development of metastasis. Therefore, the concurrent use of chemotherapy in a case like this would not be recommended. However, if the tumor is growing rapidly, has frequent mitoses and is poorly differentiated or anaplastic, this likely represents an oral FSA case with a high-grade lesion that would be at risk for the development of distant metastasis. In contrast to cases with low-middle grade lesions, cases like these may benefit from the use of adjuvant chemotherapy to fight occult distant metastatic disease. Unfortunately, no clinical efficacy data exist concerning the use of chemotherapy in high-grade feline oral FSA. Anecdotally, these authors believe that doxorubicin and carboplatin would be expected to have the best activity against feline oral FSA, albeit the response rate would likely be low.

To the author's knowledge, no studies are presently ongoing to discern the molecular biology of feline oral FSA. This is most likely due to the paucity of feline oral FSA cases and our increased abilities to potentially garner a cure with this disease when compared to feline oral SCC. In summary, feline oral FSA are incredibly invasive, but minimally metastatic tumors that can potentially be cured via aggressive local therapies including surgery and/or radiation therapy.

Other Tumors

Though rare, a variety of other diagnoses are on the differential list for feline oral neoplasia. These include lymphoma, osteosarcoma, melanoma, chondrosarcoma, granular cell tumors, fibropapillomas, hemangiosarcoma, ameloblastomas and

fibromatous or ossifying epulides [20-25]. While other tumors such as inductive fibro-ameloblastoma ("feline inductive odontogenic tumor") and calcifying epithelial odontogenic tumor ("amyloid-producing odontogenic tumor") have been reported, this has become an area of controversy as other reports suggest both of these tumors should be simply classified as ameloblastomas [26-29]. The prognosis for cats with oral lymphoma or hemangiosarcoma is presently unknown because it is such a rare site of involvement, however, the use of local therapy (surgery and/or radiation therapy) and adjuvant chemotherapy would be recommended due to its aggressive local and systemic phenotype. The other tumors listed above would be generally thought of as locally aggressive, but minimally to non-metastatic tumors, suggesting that aggressive local therapy would have a high chance of being curative.

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