Nasal Adenocarcinoma in the Canine

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Introduction

Neoplasms of the nasal and paranasal sinuses make up approximately 1% of canine tumors.[1-5] These tumors are malignant in 80% of the cases, and 60-75% are carcinomas.[2,6] According to most authors, adenocarcinomas are the most common nasal tumor, followed by squamous cell carcinoma. Large and medium sized dogs in the 8-10 year age group are most commonly affected. Some authors find the dolicocephalic breeds to be the most prone to develop adenocarcinoma,[5,7] while others find the number of cases higher in the mesocephalic breeds.[3,4] Some reports show a higher incidence of nasal adenocarcinoma in male dogs,[5,7,8] but when correction is made for sex distribution of the number of cases seen, there is no difference in nasal tumor incidence between males and females.[2,8,6] There is no known etiological agent for nasal adenocarcinoma, and there is no difference between urban and rural dogs with respect to nasal and sinus neoplasia.[5,9]

Nasal adenocarcinomas are primary tumors of the respiratory epithelium covering the respiratory portion (maxilloturbinates, ethmoturbinates, nasoturbinates, and nasal septum) of the nose[10] which kill by local invasion; metastasis is rare. Unfortunatley, early diagnosis and treatment is difficult to accomplish because clinical signs appear only after the tumor is fairly well advanced. Treatment of this type of tumor has not been very successful, and the mortality rate associated with nasal and sinus adenocarcinoma is quite high.[1,7] With conventional treatments, mean survival times are reported at 4-6 months.[4,6,7,8]

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Theories of Carcinogenesis

The basic cellular events in neoplastic transformation are similar whether transformation is brought about by chemical, radiation, physical, or viral agents. Therefore, although the etiology of nasal carcinoma is unknown, a general discussion of carcinogenesis is still pertinent. All of these cellular events change nuclear DNA in such a way that it can be transmitted from a cell to its daughter cells.

Carcinogenesis appears to be a multi-staged process. The transformation or "initiation" stage is followed by a "promoting" event which allows the potentially neoplastic cell to proliferate. Promoting factors include local tissue injury or hormonal influences which stimulate cells to divide. They may also include impaired immunological function in which transformed cells, normally kept in check by the immune response, may proliferate unchecked. For example, radiation, through its ability to cause local tissue damage as well as immune suppression, may serve as both initiator and promoter of neoplastic transformation.[10]

There are many reports of chemically-induced tumor formation in animals. The carcinogenicity of nitrosamines is due to tissue conversion to carcinogenic metabolites. The nasal mucosa is a site with marked nitrosamine metabolizing capacity.[10] In addition to a local carcinogenic effect, parenterally administered nitrosamines are transported in the bloodsteam to the nasal cavity.[11] DMCC, a carbamic acid derivative known to have carcinogenic properties, is used as an intermediate in the production of certain carbamate pesticides.[10] HMPA (hexamethyl-phosphoramide) is used in the production of several types of plastics, and has been shown to selectively induce nasal tumors.[11]

Clinical Description

Early clinical signs of nasal and sinus adenocarcinoma are nonspecific, and most cases a veterinarian sees are already well advanced. No pathognomonic clinical pathological, physical, or radiographic signs appear until a substantial part of the nasal cavity is involved. An average of 2–6 months elapse between the onset of clinical signs and the definitive diagnosis.[3,6]

Common signs of an acute nasal tumor are unilateral nasal or ocular serous discharge, turning mucopurulent due to secondary bacterial invasion, and then proceding to hemorrhage and sneezing.[1,2,5,6,11] As the lesion progresses, the nasolacrimal duct may become obstructed[2,6] resulting in a mucoid ocular discharge. If the tumor erodes through the cortical bone of the maxilla or nasal bones, facial swelling (with or without ulceration) and distortion may result.[2,7] Ocular signs such as exophthalmos, scleral injection, and conjunctivitis result when the tumor invades the orbit in advanced cases.[1,2,6] Often, the nasal discharge has a fetid odor from necrotic tissue.[9] The animal may paw at its nose, presumably from the pain associated with a rapidly growing tumor in a small, enclosed area.[7] The tumor may invade the cranial cavity, in which case neurological signs such as violent seizuring can occur.[7,9]Differential diagnoses include a chronic rhinitis secondary to infection or trauma, foreign body lodged in the nasal cavity, fungal disease, tooth root abscess, and in certain geographical areas, *Linguatula serrata* or *Pneumonyssus caninum.*

Diagnosis

Physical examination of the nasal passages is best done while the animal is under general anesthesia. An otoscope works well to evaluate the rostral third of the nasal cavity. Intranasal neoplasia rarely involves this part of the nasal cavity even in advanced cases, but anterior rhinoscopy can help to eliminate nasal foreign body as the cause of the observed clinical signs. Rhinoscopy of the posterior nasal cavity can be accomplished using a dental mirror and a good light source, after the soft palate is retracted rostrally. This examination aids in ruling out abnormalities such as soft palate polyps and nasopharyngeal tumors in the caudal nasal cavity.[1]

Nasal washings with saline allow one to get a sample for cytological examination. The dog is put in lateral recumbency with the affected side down. An endotracheal tube with an inflated cuff is used to prevent excess fluid from reaching the lower airways. A flexible tube is attached to a 35cc syringe, and 5–10cc of saline is flushed through the nares, or from behind the nasopharynx, using alternating positive and negative pressure. This procedure may have to be repeated several times to get enough cells for cytological evaluation.[8] Some workers[5,7] have obtained false negative results with this procedure, and diagnosed non-malignant inflammatory changes only to have later biopsy results indicate malignant adenocarcinoma. This is not surprising since most tumors have reactive tissue in their matrix, especially in the peripheral areas of the tumor.[7,9] If neoplastic cells are seen, a positive diagnosis can be made.

Bacterial, mycotic, and yeast cultures should always be done, keeping in mind that bacteria isolated from the nasal cavity may be part of the normal flora (especially if a mixed culture is obtained) or may be secondary to the presence of a foreign body or tumor. Under these circumstances, antibiotics will not cure the secondary rhinitis, although a temporary response may be seen.[1,2] Positive bacterial cultures are obtained in over 60% of the nasal discharges cultured, with a variety of organisms recovered (i.e. coliforms, streptococcus, staphylococcus).[2] Of the fungal diseases which affect the nasal cavity and sinuses, aspergillosis is most common, with blastomycosis, cryptococcosis, and nasal penicilliosis occurring less frequently.[2]

The lesion can be biopsied either through a surgical approach through the nasal bones prior to curettage of the sinuses and/or nasal cavity, or by introducing a large-gauge polypropylene urinary catheter into the nose. The catheter is cut at a 45° angle to form a sharp cutting edge. The catheter is advanced into the site of the lesion via an otoscope speculum, and suction is applied using a 12cc syringe. Plugs of tissue can be obtained in this manner. The cell type which is the origin of the nasal tumor is impossible to determine, as all of the mucosa of the nasal cavity and sinuses consists of pseudostratified columnar epithelium, and both mucous and serous glands are found beneath the basement membrane. Malignant epithelial neoplasms originating in the nasal cavity could conceivably have originated from any of these normal

structures.[6]

Perhaps the most reliable way of diagnosing an advanced nasal neoplasm is by radiography. The animal should be under general anesthesia, and in addition to the routine ventrodorsal and lateral projections of the skull, frontal sinus, open-mouth and intraoral nonscreen films should be taken.[1,2,5] A consistent sign of an early nasal epithelial cell tumor is a unilateral increased soft tissue density of the turbinates which results in a loss of the fine trabecular pattern of the normal turbinates.[1,2,5,6,7] This homogeneous density is the result of cells, debris, and fluid silhouetting with the turbinates. At this point, the appearance of the early epithelial tumor and a nondestructive inflammatory response can be similar, but as the tumor progresses, the density surrounding the turbinates becomes more heterogeneous from advancing turbinate destruction.[2] Nasal septum and vomer bone erosion can occur from a malignant neoplasm.[2,5,6,7] Destruction of overlying cortical bone is a feature of neoplastic processes.[2,6] Nasal mycosis typically results in a more lucent than normal nasal cavity as opposed to the increased density seen with adenocarcinoma. Radiographic changes suggesting a chronic inflammatory process (bacterial or allergic) include bilateral increased tissue densities, exaggerated or coarse trabecular turbinate changes, minimal alterations in overlying bone and complete or partial resolution of the lesion on serial radiographs.[2]

Therapy

The total physical status of the animal must be considered before any type of therapy is undertaken. All forms of cancer therapy are toxic to some degree and it is the veterinarian's responsibility to ascertain if the patient can survive therapy. A CBC and blood chemistries should always be run before a treatment regime is started. The frequency of administration may also be a factor to be considered if the treatment, e.g. radiotherapy, is located a great distance from client's home. The client should also be forewarned that follow-up visits will be necessary to monitor therapeutic results.

Surgery is perhaps the first therapy considered when nasal or sinus adenocarcinoma is strongly suspected or diagnosed. However, its value is in allowing the surgeon to "debulk" the tumor and in providing biopsy specimens. Surgery as the sole therapy for a nasal tumor offers no benefit for long-term survival.[5,7,8,12,13,2] The procedure consists of removing a dorsal flap of bone from the nasal and maxillary bones which may or may not be replaced.[1,2,7,8,9,14] If the excised bone is not replaced it is imperative that the periosteum be preserved to facilitate obtaining an airtight closure. Once the cavity or sinus is exposed, radical excision and curettage of the neoplasm is attempted. The nasal turbinates and septum are removed when necessary.[8,12]

Cryosurgery is performed after routine surgery and curettage of the nasal cavity.[1,8] Liquid nitrogen can be sprayed or poured on the area to be frozen, but it is probably better to avoid the latter method as the amount of freezing is more difficult to control. Thermocouples are placed outside the maxillary bones and below the hard palate to estimate the depth of freezing. Using a commercially available cryosurgery unit, the maxillary bones, bony orbit, cribriform plate, and frontal sinuses can be frozen. The hard palate should be frozen with caution, as the mucosal covering of the roof of the mouth can be damaged. The theory behind cryosurgery is that rapid freezing ($-20°C$) and slow thawing destroy viable tumor cells that are still left after curettage. The frozen bone dies but remains in place as an autogenous bone graft, allowing revascularization and new bone growth.[8,12]

Hyperthermia is an alternate method of killing residual tumor cells after the nasal cavity and/or sinuses are curetted, or in conjunction with radiotherapy. Advocates of hyperthermia state that 1) heat suppresses the ability to repair radiation damage; 2) heat enhances the expression of lethal radiation damage; 3) tumor cells may be more heat-sensitive than normal cells; and 4) hypoxic cells are more heat-sensitive than aerobic cells.[15] High frequency current (500 KHz) with direct or capacitative coupling is applied to the tumor. Intratumor temperatures are monitored using 26ga needle thermistor probes.[14]

Radiotherapy is one of the more commonly used therapies as an adjunct to surgery,[3,4,6,7,8] cryosurgery,[4] or hyperthermia.[14] Although many believe that radiotherapy coupled with surgery offers the best way to manage nasal tumors[2,4,6,8] and may prolong the lifespan of the dog 5–14 months longer than surgery alone,[15] a drawback is that the equipment re-

quired is usually available only at universities. Also, treatments are expensive and often done on a Monday/Wednesday/Friday schedule for a period of up to 3 weeks, necessitating frequent trips by the client to the treatment facility.[4,6,8] Radiation is delivered either by using orthovoltage X-rays, or by using Cobalt or Cesium to deliver gamma radiation.

Immunotherapy or immunopotentiation is an attempt to enhance the body's own immune response to disease. It can be used alone or as an adjunct to other therapy.[8] One treatment is adjuvant therapy using levamisole, BCG (Bacillus Calmette-Guerin), or mixed bacterial vaccine (MBV).[8,15] Administered parenterally or intralesionally, this entails fairly long-term treatment, and not all workers are convinced of its efficacy.[2,15] Major side effects are fever, chills, nausea, and vomiting.[15]

Tumor-specific vaccines have been used against some carcinomas.[15] Tumor cells are taken from the patient's tumor and modified by various techniques in order to kill the cells but hopefully maintain their antigenicity. However, it is unlikely that tumor vaccines will become commonplace in veterinary medicine due to difficulty in preparing the vaccine.

Chemotherapy is another method of managing nasal adenocarcinoma in the dog. There are over 20 anti-cancer drugs commercially available,[15] all of which work at a specific stage of cell division or interfere with specific cellular reactions to slow down or stop tumor cell proliferation. Drug dosages are frequently expressed in mg/M^2 of body surface area, as this correlates well with such physiological parameters as blood volume and urea clearance. Conversion tables are available for converting mg/kg dosages into mg/M^2 dosages, as well as for converting kg of body weight into M^2 of surface area.[5,15]

Most chemotherapeutic drugs are toxic to all dividing cells, and there can be a fine line between therapeutic and toxic doses. Therefore, it is essential that all animals undergoing chemotherapy be closely monitored for toxic side effects, because most patients with neoplasia are older animals. Monitoring should consist of physical examinations, CBCs and serum chemistries, and renal function tests every 7–10 days.[8,15]

Drugs used clinically in treating adenocarcinomas include triethylene-thiophosphoramide (Thio-TEPA®), fluorouracil, actinomycin D, doxorubicin (Adriamycin®), bleomycin, and L-phenyulalanine mustard.[4,15] No one drug has shown to be very efficacious in treating nasal tumors. A pilot study for the efficacy of thioproline was recently conducted at ISU.[16] Although it was deemed doubtful that thioproline has significant cytostatic activity, it decreases epistaxis (which often results in the decision to euthanize the animal) by interfering with tumor vascularization. No toxicosis from drug administration was found, but pain and abscessation at injection sites were frequent complications.

Conclusion

Although the overall incidence of nasal adenocarcinoma in the canine population is not high, it is a highly malignant tumor in which early diagnosis and treatment is necessary. Nasal tumors should always be considered in mid-to large-breed dogs with a history of insidious onset of dyspnea, nasal discharge (especially epistaxis), and sneezing.

At the present time, the best means for managing canine nasal tumors appears to be a combination of surgery and radiotherapy. Owners must be made aware that treatment of advanced nasal carcinoma is only palliative and helps to relieve the symptoms. There is no cure for nasal adenocarcinoma, and most patients die or are euthanized within 12 months of diagnosis.

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