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INTRATHORACIC NEOPLASMS IN THE DOG AND CAT

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INTRODUCTION

Neoplasms of the thoracic cavity are as diverse as the structures and tissues that comprise the thorax. Intrathoracic masses may represent neoplastic disease of a localized structure such as the thymus, trachea, esophagus, heart, and lung, or a local manifestation of a generalized neoplastic process such as malignant lymphoma. The large surface area, 60 to 90 m^2 in man, represented by the respiratory epithelium and associated thoracic structures are ideal targets for carcinogens carried by inspired air. Very little is known regarding the epidemiology, etiology, and mechanisms of spontaneous intrathoracic neoplasia in companion animals. Much of what we know or suspect about thoracic neoplasia in animals has been extrapolated from experimentally-induced neoplasms. Most studies of thoracic neoplasia have focused on the pathology of primary and metastatic neoplasms of the lung with little attention given to diagnostic and therapeutic considerations. Although the cited incidence rate for primary respiratory tract neoplasia is low, 8.5 cases per 100,000 dogs and 5.5 cases per 100,000 cats, intrathoracic masses often attract attention out of proportion to their actual importance since they are often readily visualized on routine thoracic radiographs.

EPIDEMIOLOGY

Unlike their human counterparts in which thoracic neoplasia, particularly lung cancer, is a major cause of death, intrathoracic neoplasia in domestic animals is an unusual cause of death. Primary pulmonary neoplasms are uncommon in dogs, cats, and horses, representing approximately 1% of all neoplasms in these species. The prevalence of primary lung tumors is 4.17 cases/100,000 dogs, according to one study. Although an increase in the number of primary lung tumors in dogs over the last 20 years has been reported. It appears to be a disease of middle age with most tumors occurring during the second decade of life. There is limited evidence to implicate environment or owner occupation as factors in the development of intrathoracic neoplasms in animals.

GEOGRAPHIC VARIATIONS

Few studies have attempted to link the distribution of canine and feline respiratory neoplasms to environmental distribution. In one study, the environment was roughly divided into urban and rural areas based on atmospheric pollution and industrialization concentration around a major metropolitan area. While no significant differences were noted in the patient distribution between urban and rural areas for respiratory cancer in that study, it didn't rule out the potential usefulness of animals as comparative models for environmental health or for being at risk along with human subjects.

GENETIC AND INTRINSIC FACTORS

Genetic and intrinsic factors have been implicated in the pathogenesis of intrathoracic neoplasia. For example, pre-existing skeletal abnormalities such as multiple exostoses or osteochondromas in man have reportedly progressed to chondrosarcomas, whereas malignant transformation to both chondrosarcoma and osteosarcoma has been reported in the dog and cat. Familial aggregation of osteosarcoma has been described in St. Bernards. Specific breed predispositions for neoplasms arising within the thoracic cavity include: 1) thyroid carcinoma in boxers, golden retrievers, and beagles; 2) neoplasms of the chemoreceptor system in certain brachycephalic breeds; and 3) cardiac hemangiosarcomas in German shepherd dogs. There is no apparent sex predilection.

ETIOLOGY

In contrast to human subjects, where smoking is clearly the single biggest cause of respiratory neoplasia, few risk factors have been clearly defined in domestic animals that can be pointed to as primary causes of intrathoracic carcinogenesis. There are however several factors, such as ionizing radiation, chemicals, viruses, and environmental and occupational causes, that have been implicated in both spontaneous and experimentally-induced disease.

MECHANISMS OF CARCINOGENESIS

Carcinogenesis involves a complex interplay of heredity and environment. If there is a unifying principle, it is that carcinogenesis is a multistage process. Most experimental and epidemiological data are consistent with a two-stage model for the pathogenesis of cancer. This view is supported by the classical initiation-promotion experiments of Berenblum and Shubik, the occurrence of tumors in two forms, one not inherited and the other inherited in an autosomally dominant fashion, and the observation that in hereditary neoplasms the inheritance of the gene is not sufficient as the cellular level to give rise to cancer. According to the two-stage model, the first mutational event leads to an improperly controlled proliferation of cells that have sustained that event. After the second event has occurred, the cell is committed to developing into a clinically apparent cancer. Despite the importance of the steps that lead to cancer, until recently neither the number of steps nor their nature was known for any neoplasm.

Recent advances in molecular biology have allowed the elucidation of the molecular events involved in the development of solid tumors. These techniques have demonstrated that these neoplasms develop by a stepwise accumulation of several mutations, some of which activate oncogenes that push cells toward the cancerous state while others inactivate genes that suppress tumor growth (tumor suppressor genes, anti-oncogenes). This stepwise progression has been most clearly demonstrated for colon cancer in man, but it may represent a model of genetic carcinogenesis applicable to many neoplasms regardless of site of origin. This series of genetic changes includes: point mutations, chromosomal rearrangements and deletions, gene amplifications, and changes in gene expression. The target genes include dominant acting cellular oncogenes, putative recessive genes uncovered by deletions, and genes for growth factors and/or their receptors, especially the so-called autocrine growth factors produced by the cancer cells themselves.

Radiation-induced and spontaneous lung cancers in beagles have been studied in order to identify the number and nature of the specific cellular changes involved in the stepwise progression of normal cells to neoplasia. Available data appears to fit the two-stage model. Radiation produces DNA strand breaks and chromosomal aberrations consistent with deficient DNA repair and activation of proto-oncogenes to active oncogenes by deletion, translocation, or other gross chromosomal rearrangement. There is a strong association between inflammation, proliferation, and subsequent carcinogenesis. Studies with tumor tissue, taken from both radiation-induced and spontaneous tumors, have shown that the DNA contained tumor-specific restriction fragment-length polymorphisms associated with H-ras, K-ras, erb B, src, v-ros, c-met, and myc oncogenes. Normal homologues for some of these genes are receptors for growth factors, and deregulation of these genes may play a major role in growth regulation (proliferation) of these cells. Another important mechanism by which cell growth may be deregulated is through the conversion of various growth factors and/or their receptors to oncogenes. These factors can stimulate or inhibit cell proliferation by paracrine or autocrine pathways, and overexpression of these factors may confer a proliferative advantage to initiated or neoplastic cells. Epidermal growth factor receptor (EGFR), epidermal growth factor (EGF), transforming growth factor-alpha (TGF-α), insulin growth factor-1 (IGF-1), and bombesin appear to be overexpressed in both radiation-induced and spontaneous lung tumors in beagle dogs. However, the significance and time-course of these molecular mechanisms in the genesis of thoracic neoplasia is still unclear at present.

CLINICAL SIGNS

Intrathoracic neoplasms can manifest themselves in many way depending on location of the tumor, rate of growth, cell type, presence of previous pulmonary or cardiac disease, presence of a paraneoplastic syndrome, and awareness of the animal owner. Many patients may remain asymptomatic for months or years before exhibiting clinical signs. These animals are often recognized incidentally during radiographic examinations for other problems. The most frequent signs of intrathoracic neoplasia are cough and dyspnea. Other signs can include a change in voice, wheezing, blood-tinged sputum or hemoptysis, fever, weight loss, dysphagia, edema of the head and neck, ascites, lameness, cyanosis, and collapse.

DIAGNOSTIC APPROACH

Beyond a complete history and physical examination, thoracic radiography remains the first step in patient evaluation. Although thoracic radiographs are unlikely to yield a definitive diagnosis of neoplasia, they are of value in determining the extent of the lesion and the course of subsequent diagnostic procedures. The same can be said of ultrasonography which is even more likely to yield information regarding the site and extent of the intrathoracic lesion. If therapy is contemplated, then it is important to establish a precise histologic diagnosis since the therapeutic approach to non-small cell lung cancers and small-cell lung cancers in human patients is substantially different. There are a number of standard and several new diagnostic procedures that can yield clinically useful results without having to resort to thoracotomy. Observations on serial cytologic findings in the sputum of uranium miners, showed that cellular changes indicating carcinoma were present before cancer became clinically evident. Collection of sputum is difficult in animals, and cytologic specimens are usually obtained by other methods such as transtracheal aspiration or bronchoscopy. If pleural fluid is present, then thoracentesis can be employed to improve the patient's respiratory status, to collect a sample for fluid and cytologic analysis, and to facilitate radiographic evaluation of thoracic structures. Those masses that cannot be diagnosed by minimally invasive methods are candidates for percutaneous biopsy or aspiration to obtain suitable specimens.

Closed biopsy utilizing fluoroscopy or ultrasonography to guide the operator can have a high diagnostic yield and may provide a definitive diagnosis. Thoracotomy is reserved for those patients with undiagnosed intrathoracic disease or those with a mass lesion for which aggressive treatment is intended.

CLINICAL STAGING

The World Health Organization TNM system of classification of neoplasms in domestic animals is recommended for the clinical staging of intrathoracic neoplasms. The staging process in human patients is enhanced by the availability of imaging techniques. Advances in medical imaging such as computer tomography (CT), magnetic resonance imaging (MRI), and spectroscopy (MRS), single photon emission computed tomography (SPECT), and positron emission tomography (PET) have led to dramatic improvements in the ability to diagnose and monitor human cancer. Although most of these techniques are not available to veterinary patients, some of the larger referral centers have the ability to do cross-sectional imaging. The primary role of cross-sectional imaging in the staging process is the identification of abnormal intrathoracic lymph nodes. In the absence of imaging capability, evaluation of intrathoracic nodes can be accomplished via radiographs and direct examination and biopsy during thoracotomy. Anticancer targeting systems which employ either monoclonal antibodies, growth factors, cytokines, or synthetic peptides that can selectively recognize and specifically bind to malignant cells represent new technologies in cancer diagnosis, staging, and therapy. These systems can be used to preferentially target tumor sites for imaging/therapy while sparing normal tissues and minimizing adverse effects. The overexpression of growth factors in both radiation-induced and spontaneous lung tumors in dogs suggests that these systems could be used to advantage in veterinary oncology.

TREATMENT

Surgery remains the treatment of choice for intrathoracic neoplasms in the dog and cat. This option is limited by the occurrence of multiple intrathoracic masses, metastasis to intrathoracic lymph nodes or extrathoracic sites, and poor medical status of the patient. Radiation therapy of intrathoracic neoplasms has rarely been attempted in the dog and cat although several tumors such as thymoma, malignant lymphoma, and carcinomas are known to be relatively radiosensitive. Its usefulness is limited by radiation pneumonitis and esophagitis, bone marrow suppression, skin and haircoat changes. Adjuvant chemotherapy for intrathoracic neoplasms has received little attention in veterinary medicine, with the possible exception of those animals with the anterior mediastinal form of malignant lymphoma. However, the rationale for adjuvant chemotherapy for intrathoracic tumors is enhanced by the emergence of newer drugs and drug combinations that appear to be achieving higher response rates in veterinary patients. Chemotherapy can be used for patients with multicentric intrathoracic cancer for palliation or cure, or as an adjunct to surgery if pathologic evaluation of tissues obtained during thoracotomy suggests extension of the disease beyond the primary site or incomplete removal of the tumor itself. Cisplatin, doxorubicin, mitoxantrone, vincristine, and cyclophosphamide have been infrequently used, either singly or in combination, to treat primary or metastatic lung cancer in animals. Given the advanced stage at which intrathoracic cancer is usually diagnosed in domestic animals, aggressive multimodality therapy such as chemoradiation or intensive polychemotherapy is probably warranted for patients with extensive disease.

Adoptive immunotherapy has also been evaluated in treatment of dogs with lung tumors. Prior to treatment, the ability of peripheral blood lymphocytes (PBL) to differentiate ex-vivo in the presence of human recombinant interleukin-2 (rIL-2) and become tumoricidal was investigated. PBL were grown in the presence of RIL-2 to generate lymphokine-activated killer (LAK) cells, or with phytohemagglutinin (PHA) and rIL-2 to generate autologous-stimulated lymphocytes (ASL). Results showed that ASL were more cytolytic than LAK against all target cells ex-vivo suggesting that ASL may be more beneficial than LAK for immunotherapy of canine tumors.

PROGNOSIS

There is limited information available on prognostic factors for intrathoracic neoplasms in the dog and cat. For dogs with primary pulmonary neoplasms, lymph node involvement appeared to be the most important prognostic indicator. In human patients with lung cancer and dogs with spontaneous and radiation-induced lung cancers, survival has been correlated to tumor doubling time (TDT). Therefore, it is important to take two radiograph views (dorsoventral and lateral) of the thorax in order to obtain two-dimensional measurements that can be used to calculate tumor volume. If surgery is not attempted in these patients, the TDT can be used to monitor response to therapy or project the time to recurrence if therapy is discontinued.

SUMMARY

All too often, a diagnosis of intrathoracic neoplasia results in euthanasia due to a perceived lack of therapeutic options and difficulties inherent to arriving at a definitive diagnosis. As the use of newer diagnostic procedures, radiotherapy, and chemotherapy becomes more available and accepted in veterinary medicine, we should be able to offer our patients with intrathoracic neoplasia a variety of positive choices that will enhance their quality of life and improve their chances for survival. The practitioner is encouraged to consult with a veterinary oncologist concerning possible clinical trials or newer drug combinations that may benefit selected patients.

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