Canine Nasal Adenocarcinoma

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Introduction

In dogs, tumors of the nasal cavity and paranasal sinuses are rare, comprising about 1-2% of all reported canine neoplasia.[1,2] Excluding tumors of the nasal planum, approximately two-thirds of nasal tumors are carcinomas, with the majority of remaining nasal tumors being sarcomas.[3] The most common nasal tumor in dogs is the adenocarcinoma.[4] Nasal adenocarcinomas are considered to be malignant primary tumors that arise from the respiratory epithelium and associated structures inside the nose.[5] Local invasion of the tumor is aggressive and expands into surrounding tissues and bone. Adenocarcinomas most frequently occur within the lumen of the nasal cavity and can extend through the subcutaneous tissue, hard palate, cribriform plate, or nasal bones into the oral cavity and calvarium. The rate of metastasis has been characterized as low, with a 10% metastatic rate at the time of diagnosis and approximately 40-50% metastatic rate at the time of death.[2] The most common sites for metastasis are the local lymph nodes, such as the submandibular nodes, and the lungs. Less commonly, nasal adenocarcinomas metastasize to the skin, liver, kidneys, bone marrow, or central nervous system. The average age at diagnosis for canine nasal adenocarcinoma is 10 years, with a slight predilection towards males. It has also been more commonly reported in medium-to-large breed dogs. Clinical signs of nasal adenocarcinoma depend on the stage of the disease, but can include lethargy, anorexia, weight loss, sneezing, nasal discharge, epistaxis, ocular discharge, exophthalmos, regional lymphadenopathy, and facial deformity. Treatment of canine nasal adenocarcinoma focuses on local control of the tumor through palliative care, surgery, radiation, or chemotherapy. Due to non-specific clinical signs and the locally-invasive nature of the disease, diagnosis and treatment can present a significant challenge for both veterinarians and owners.

History

Izzy Cooper, a 9-year-old female spayed rat terrier, presented to the MSU-CVM Internal Medicine Department on September 8th, 2017 after referral for a two-week history of unilateral epistaxis and sneezing. The owner reported that Izzy would sneeze multiple times daily with intermittent serous to bloody nasal discharge, especially after rolling in the grass outside. She was seen by her primary veterinarian on September 1st, 2017, one week prior to presentation at MSU-CVM, and had several diagnostic tests performed. Samples were submitted for complete blood count, serum chemistry, total T4, D-dimer, fibrinogen, clotting times, and an aspergillus antibody test. Bloodwork revealed a severely elevated alkaline phosphatase, severe hypoglycemia (determined to be artifact), mild leukocytosis characterized by absolute neutrophilia, mildly decreased hemoglobin, and mildly decreased hematocrit. Fibrinogen concentration was mildly elevated. Clotting times, D-dimers, total T4, and aspergillus antibody tests were found to be within normal limits. The referring veterinarian began empirical treatment with a seven-day course of chlorpheniramine, enrofloxacin, deracoxib, oclacitinib, and prednisone. On recheck examination, Izzy was reported to be unresponsive to medications with a static progression and was then referred to MSU-CVM for further workup.

Presentation

Upon presentation, Izzy was quiet, alert and responsive. She was overweight at 6.0 kilograms with a body condition score of 6/9. She was slightly tachycardic at 150 beats per minute with strong, synchronous femoral and digital pulses. Izzy was tachypneic with a respiratory rate of 42 breaths per minute. Rectal temperature was normal at 101.4°F. Her mucous membranes were pink with a capillary refill time of less than 2 seconds. Physical examination revealed epistaxis at the right nostril, crusting at the left nostril, a painful soft-tissue bulge

between the eyes, a flat and firm mass along the cranial sternum, and pain on ocular retropulsion bilaterally. Further evaluation revealed decreased bronchovesicular sounds on the left, tracheal wheezes, a painful abdomen, and severe dental disease. Her oxygen saturation measured at 100% on room air and electrocardiogram showed a normal sinus rhythm. Multiple non-invasive blood pressures were measured at 181/107 (144), 184/97 (126), 180/96 (124). FAST scan of the abdomen was unremarkable, but FAST scan of the thorax revealed pleural effusion on the left side and an intrathoracic mass.

Differential Diagnoses

Due to the soft-tissue mass replacing bone between the eyes and the concurrent intrathoracic findings, nasal or paranasal neoplasia was our primary differential with potential secondary pulmonary metastasis. Fungal rhinitis was still a consideration, but the negative aspergillus antibody test performed by the referring veterinarian reduced our clinical suspicion. The top differentials for canine nasal neoplasia are adenocarcinoma, squamous cell carcinoma, fibrosarcoma, osteosarcoma, and chondrosarcoma. Other less common differentials for nasal neoplasia are lymphoma, mast cell tumor, transmissible venereal tumor, hemangiosarcoma, neurofibrosarcoma, leiomyosarcoma, rhabdomyosarcoma, fibrous histiocytoma, and undifferentiated sarcoma or carcinoma.[6] In Izzy's case, further diagnostic tests were required to make a definitive diagnosis of nasal neoplasia and to understand the prognosis and treatment options available.

Pathophysiology

The pathophysiology of all neoplasia is due to uncontrolled cell growth and proliferation secondary to genetic changes within the cell. The nomenclature for the type of neoplasia is dependent upon the cell line from which the tumor arose. Carcinomas are defined as neoplasia of

epithelial cells, where the prefix “adeno” denotes neoplasia arising from glandular tissue.[7] Therefore, nasal adenocarcinomas are a malignant neoplasia that result from uncontrolled cell growth and proliferation of the nasal or paranasal glandular respiratory epithelium. As a malignant, locally-invasive tumor, nasal adenocarcinomas cause progressive destruction of soft tissue and bone extending throughout the nasal cavity.[2] Since they are slow to metastasize, the majority of morbidity associated with adenocarcinomas is due to uncontrolled or recurrent local disease. No definitive etiology has been described for nasal adenocarcinomas, though several predisposing risk factors have been studied. No definitive associations have been proven, but there may be increased incidence in dolichocephalic breeds, urban areas with high amounts of air pollution, chronic secondhand tobacco smoke exposure, or secondary to inhalation of combustion byproducts.[8,9] In limited studies, nasal adenocarcinomas have demonstrated molecular changes such as overexpression of p53 tumor suppressor protein in 57% of cases and expression of COX-2 in 81% of cases.[10,11,12] More studies are warranted to further classify involved oncogenes and tumor suppressor genes that may influence the growth and behavior of nasal adenocarcinomas.

Diagnostic Approach & Considerations

Diagnosis of nasal adenocarcinomas can be challenging early in the course of disease where non-specific clinical signs such as nasal discharge or sneezing dominate. Later in the course of the disease, diagnosis can be much easier due to progression of clinical signs to facial deformity, exophthalmos, or neurological signs with invasion into the cranial vault.[2] A thorough history often leads to suspicion for nasal disease and further workup is required for definitive diagnosis. Physical examination should focus on characterizing nasal discharge (if present), palpation of bony facial structure, thorough oral examination, nasal cavity patency, and ocular

examination. Complete blood count and serum chemistry should be performed to rule out comorbidities, but do not routinely show consistent signs between cases. If epistaxis is present, tests for hypertension, coagulation factors, and clotting times should be performed. Additionally, blood should be submitted for aspergillus serology to rule out fungal rhinitis as a differential. Evaluation of the nasal cavity by diagnostic imaging should always be performed. Skull radiography is a highly-sensitive and widely-available diagnostic tool for evaluation of the nasal cavity. Radiographic signs consistent with intranasal neoplasia include increased soft tissue density from the expanding tumor (often unilateral), loss of bony trabecular pattern from lysis, and displacement of midline structures.[2] However, radiographic interpretation can be challenging due to superimposition of structures, the absence of midline displacement, and the complexity of nasal anatomy. Thoracic radiography should be performed after diagnosis of a nasal mass for staging purposes, though metastasis is uncommon at the time of diagnosis. Computed tomography and magnetic resonance imaging are excellent alternatives to radiography and can determine the full extent of the nasal tumor and associations with the sinuses, ocular orbit, cribriform plate, or cranial vault. These diagnostics are more expensive and less available than skull radiography. Rhinoscopy is another alternative that may be employed to allow visualization and assist in biopsy of the nasal tumor. Regardless of imaging modality, definitive diagnosis of the type of nasal tumor present requires cytologic or histologic examination of tumor tissue. Many techniques are available for sampling intranasal neoplasia and include direct swab, nasal flushes, fine-needle aspiration of facial deformities, blind biopsy, rhinoscopy-guided biopsy, closed suction biopsy, or surgical incisional biopsy. The most consistently successful technique for definitive diagnosis is biopsy for histological examination.[2]

Treatment & Management

Treatment for canine nasal adenocarcinoma is primarily directed at local control of the tumor, but can be difficult due to invasiveness, inaccessibility, and proximity to the brain and eyes. Curative treatment is rare regardless of treatment modality, but can increase the survival time and quality of life for the patient. The treatment of choice for intranasal tumors is radiotherapy.[2]

Surgery has been pursued in the past as a primary method for gaining disease control, but is often ineffective due to early and aggressive bony invasion and high rate of recurrence. Dorsal rhinotomy for surgical access is the most common technique, but is often reserved for collection of tumor tissue after non-diagnostic biopsies. Surgical debulking may also be performed, but decreased ability to gain clean margins means that curative surgery is highly unlikely. Additionally, surgery is associated with a high rate of morbidity, increased cost, and no improvement in median survival times. Median survival times identified for all malignant intranasal carcinomas following surgery alone are between 3-6 months, which are similar to the median survival time of benign neglect. In a very limited study, cytoreductive surgery combined with radiotherapy offered a median survival time at 47 months, but carried a high long-term complication rate of nearly 40%.[13]

Radiotherapy, as the treatment of choice, is often used alone as a treatment for nasal adenocarcinoma. Although radiation is unlikely to be curative, symptom-free survival times and median survival times are most improved with radiotherapy. Treatment options are generally divided into definitive or palliative treatment protocols. Definitive protocols are used to maximize tumor destruction through daily treatment with high radiation doses delivered over the course of several weeks. Palliative protocols are used to decrease clinical signs associated with the tumor and improve the quality of life for the animal through weekly to biweekly treatments

with a lower radiation dose. Based upon the treatment protocol employed, both acute and late-term side effects can be seen. Acute effects due to local toxicity of the skin, nose, and eyes are more common with definitive treatment protocols and include local alopecia, erythema, mucositis, rhinitis, moist desquamation, blepharitis, and keratoconjunctivitis sicca. Supportive care is often successful at managing acute side effects. Late effects can present as ocular, neurologic, osseous, or dermal disease secondary to destruction of slowly-dividing cells, but many animals die from the disease before development of these clinical signs. Therefore, the efficacy of radiotherapy is limited by how the patient responds and the toxicities associated with treatment. Median survival times with definitive protocols are between 20 and 25 months with a 1-year survival rate around 50%.[13,14]

Chemotherapy has been utilized as a treatment modality for nasal adenocarcinomas, but generally has minimal efficacy. Multiple chemotherapeutic protocols have been described, but are rarely curative when used as a sole treatment. As such, chemotherapy is often used as rescue after radiotherapy failure or to treat metastatic disease. However, in cases with metastatic disease, prognosis is poor to grave and therapy is rarely pursued. Since nasal adenocarcinomas may exhibit production of COX-2, piroxicam has been implicated as an adjunctive treatment to achieve improvement in clinical signs, but requires further study to determine its efficacy.[10]

Case Outcome

In Izzy's case, after she was assessed and determined to be stable, an intravenous catheter was placed and blood was sampled for a current coagulation profile and complete blood count. Clotting times were within normal limits and the complete blood count revealed mild decreases in hemoglobin, mean corpuscular hemoglobin concentration, hematocrit, and packed cell volume. A mild neutrophilia and moderate lymphopenia were also discovered. Izzy was then

taken for a series of thoracic radiographs that revealed moderate pleural effusion in the left thorax, atalectic left lung lobes, multiple mineral opacity masses within the cranial mediastinum, a mineral opacity mass in the subcutaneous space along the cranial sternum, multiple soft tissue nodules within the central and caudal lung fields, and an obscured cardiac silhouette. Severe pulmonary metastases were diagnosed based on clinical signs and radiographic evidence. The owners were notified and elected for humane euthanasia with necropsy. Since definitive diagnosis had not been made, a post-mortem fine needle aspiration of the soft tissue mass between her eyes and computed tomography were performed for educational purposes.

Necropsy revealed that Izzy was a very unique case in that she had two primary malignant neoplasms, one arising from the nasal cavity and the other arising from the sternum. Gross examination found the bones of the frontal sinuses and left anterior calvaria were replaced by an infiltrative, white, fibrous, unencapsulated neoplasm that extended into the caudal nasal cavity and olfactory bulb. Tissues varied from fibrous to friable and turgid. Histopathology of the nasal tumor revealed an infiltrative, densely cellular, unencapsulated, poorly demarcated neoplasm composed of epithelial cells expanding and effacing the nasal mucosa. Cells formed tightly packed lobules, irregular acini, and small fronds in delicate fibrovascular stroma. The cells also varied from columnar and simply regimented, to pleomorphic and bizarre, with abundant fine amphophilic cytoplasm and large ovoid nuclei with lacy chromatin and large central nucleoli. Anisocytosis and anisokaryosis were marked. Mitoses were frequent and abnormal. The neoplasm invaded the olfactory bulb and was heavily infiltrated by neutrophils at this site. Definitive diagnosis of primary nasal adenocarcinoma was made based on these findings.

Gross necropsy findings within the thorax included a markedly expanded mediastinum by a roughly ovoid to multinodular, fibrous, gritty, hard, white, 12x5x6 cm mass that was firmly adherent to, and infiltrated, the sternum. Hundreds of white, ovoid, slightly bulging, firm, well demarcated, 1-2mm wide foci spread up the sides of the inner thoracic wall, forming linear arrays cranial and caudal to the ribs. Several random white, spherical, 5-10mm wide, hard fibrous nodules were scattered through the lung lobes. Two nodules similar to those in the lungs were present in the liver and five nodules were present randomly in the renal cortices. Histopathology of the sternal mass revealed an infiltrative, multinodular, unencapsulated, well demarcated neoplasm composed of bone producing cells present throughout the tissues. Cells formed dense fascicles and osteoid in dense collagenous stroma, often becoming entrapped in the woven bone matrix. The cells were noted to be large and spindled with moderate fine amphophilic cytoplasm and large round nuclei with lacy chromatin and a large nucleolus. Cell variation was mild, and mitoses were infrequent. Definitive diagnosis of primary osteosarcoma arising from the sternum with secondary metastases to the lungs, kidneys, and liver was made based on these histopathologic findings.

Izzy's case is unique in that she was affected concurrently by both nasal adenocarcinoma and sternal osteosarcoma. She showed minimal clinical signs indicative of systemic metastatic disease and was primarily affected with nasal symptoms. Izzy's case exemplifies the need to perform staging tests such as thoracic radiography prior to treatment to determine comorbidities and other negative prognostic factors. Altogether, nasal adenocarcinoma is the most common nasal tumor that arises from glandular respiratory epithelium and should be considered in any middle-aged to older animal that presents with sneezing, nasal discharge, or epistaxis.

References

1. Madewell BR, et al. Neoplasms of the Nasal Passages and Paranasal Sinuses in Domesticated Animals as Reported by 13 Veterinary Colleges. *Am J Vet Res*, 1976. 37(7):851-856.

2. Morris J, Dobson J. Head and Neck. In: Small Animal Oncology. 1st ed. Blackwell Science Ltd, 2001. 94-125.

3. Duncan B, Lascelles X, White RN. Tumours of the Respiratory System and Thoracic Cavity. In: Dobson JM, Duncan B, Lascelles X. BSAVA Manual of Canine and Feline Oncology. 3rd ed. Wiley, 2011. 265-284.

4. Ogilvie GK, LaRue SM. Canine and Feline Nasal and Paranasal Sinus Tumors. *Vet Clin of North Am Small Anim Pract*, 1992. 22(5):1133-1144.

5. Tuttle LE, Grier RL. Nasal Adenocarcinoma in the Canine. *IA State Col Vet*, 1985. 47:1,8.

6. Thompson, MS. Clinical Signs Approach to Differential Diagnosis. In: Small Animal Medical Differential Diagnosis: a Book of Lists. 2nd ed. Elsevier Inc., 2018. 1-75

7. Cullen JM, Breen M. An Overview of Molecular Cancer Pathogenesis, Prognosis, and Diagnosis. In: Meuten, DJ. Tumors in Domestic Animals. 5th ed. Wiley Blackwell, 2017. 1-26.

8. Bukowski JA, Wartenberg D, Goldschmidt M. Environmental Causes for Sinonasal Cancers in Pet Dogs, and Their Usefulness as Sentinels of Indoor Cancer Risk. *J Toxicol Environ Health A,* 1998. 54(7):579-591.

9. Reif JS, Bruns C, Lower KS. Cancer of the Nasal Cavity and Paranasal Sinuses and Exposure to Environmental Tobacco Smoke in Pet Dogs. *Am J Epidemiol,* 1998. 147(5):488-492.

10. Kleiter M, et al. Expression of Cyclooxygenase-2 in Canine Epithelial Nasal Tumors. *J Vet Rad & US,* 2004. 45:255-260.

11. Mayr B, Reifinger M, Alton K. Novel Canine Tumour Suppressor Gene Mutations in Cases of Skin and Mammary Neoplasms. *Vet Res Commun,* 1999. 23(5):285-291.

12. Ramblin RM, Sagartz JE, Couto CG. Overexpression of P53 Tumor Suppressor Protein in Spontaneously Arising Neoplasms of Dogs. *Am J Vet Res,* 1997. 58(8):857-863.

. 13. Adams WM, et al. Outcome of Accelerated Radiotherapy Alone or Accelerated Radiotherapy Followed by Exenteration of the Nasal Cavity In Dogs With Intranasal Neoplasia: 53 Cases (1990-2002). *J Am Vet Med Assoc,* 2005. 227(6):936-941.

14. Thrall DE, Harvey CE. Radiotherapy of Malignant Nasal Tumors in 21 Dogs. *J Am Vet Med Assoc,* 1983. 183(6):663-666.